ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION

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FEW methods of treatment have given rise to so much discussion for so many years as has the use of anticoagulants in acute myocardial infarction. The first reports appeared in the mid '40s and heated discussions are still going on between its advocates and sceptics.

The most important contributions are generally considered to be the large series published in the United States by Wright et al. in 1948 and 1954:

Among 1031 patients divided into two groups—treated and untreated—these workers found in the treated group a decrease in the death-rate from 22% to 16%, and a decrease in clinically manifest thromboembolism from 26% to 11%. Some criticism has been raised against these findings, especially as the numbers in the two groups were different. Wright et al. admit that there may have been irregularities regarding the admission of patients on even and odd dates. Furthermore, the cases in the control group seem to have been rather more severe than those of the treated group.

During the same period several smaller series were presented, but in most of them the controls and the treated group were not strictly comparable (e.g., because they were studied at different times). Out of six studies (Glueck et al. 1948, Schilling 1950, Tulloch and Gilchrist 1950, Holten 1951, Feldman et al. 1952, Manchester and Ralkin 1954) which seem to be comparable or fairly so, a favourable effect was obtained with anticoagulants in all but one (Feldman et al.), and in this there was no effect.

Around 1955 the general view seems to have been that anticoagulants were beneficial in acute myocardial infarction, but some workers (Rytand 1951, Schnur 1953, Evans 1954, Garb 1955) still had doubts, because the basis of this treatment was somewhat uncertain.

1957 brought two further papers, one from the United States (Eastman et al.), and one from Britain (Honey and Truelove). Both compared series from different epochs, but these workers made an effort to study groups which were identical in respect of factors known to decide the acute prognosis. Honey and Truelove considered that the only effect of anticoagulants was to prevent venous thrombosis and thereby pulmonary embolism. Eastman et al. found only a slight and non-significant effect. Both pointed out that, because the treatment of acute myocardial infarction had also changed in other respects, the modest advances observed were not necessarily due to anticoagulant therapy. This view is supported by experience with " arm chair " treatment, which alone appears to reduce the mortality of acute myocardial infarction (Beckwith et al. 1954, Helander 1958).

Although according to the most recent publications the value of anticoagulants in acute myocardial infarction is still doubtful, the earlier favourable results have left their traces in medical departments all over the world, and anticoagulant therapy is usually regarded as a matter of course.

The doubt which has cropped up now and again, giving rise to repeated investigations, prompted us, six years ago, to undertake a controlled study of anticoagulant therapy.

Plan of Study

Our investigation, carried out for four years (1955-58) in four medical departments of the municipal hospitals in Copenhagen, was started on Feb. 1, 1955, when a uniform fixed plan of treating patients with acute myocardial infarction was introduced:

Each department used anticoagulants for two out of the four years, so that during each year this treatment was practised in two of the departments.

Thus, two departments had to stop using anticoagulants when the investigation started. Although we felt justified in doing this, we analysed the results after six, twelve, and eighteen months to see whether the mortality-rate or the incidence of severe thromboembolic complications had shown an alarming increase in patients not having anticoagulants. If this had happened we should have abandoned the plan, but there proved to be no reason to do so.

Diagnostic Criteria

In a study of this nature it is important to have definite criteria of the diagnosis of acute myocardial infarction. The patients we included fulfilled the following:

1. Definite electrocardiographic (E.C.G.) changes—i.e., either E.C.G. signs typical of acute myocardial infarction or signs less typical but altering from one tracing to the next, which were not due to severe extracardiac conditions, such as pulmonary infarction.

2. A typical history of pain and/or acute pulmonary œdema. A few patients had atypical initial symptoms, but in that case the E.C.G. and the clinical findings decided the ultimate diagnosis (fever, increase of the erythrocyte-sedimentation rate, leucocytosis, and course).

The serum-transaminase test was *not* used in selecting the cases, because this was not introduced until the study had been in progress for two years, and we could not suddenly alter our criteria of selection.

Anticoagulants

The anticoagulant agent was an aqueous concentrated solution of heparin, given subcutaneously (25,000 units twice daily). This was continued until the prothrombin level had dropped to below 25%, determined as the prothrombin and proconvertin (P & P) value by the method of Owren and Aas (1951). At the same time treatment with dicoumarol was started, 300 mg. on the first day, and 100 mg. on the second day, after which the dosage was adapted individually. As far as possible, the same doctor was in charge of the treatment. Anticoagulant medication was continued throughout the period of rest in bed, and for the first three days that the patient was allowed out of bed.

Anticoagulant treatment—or no anticoagulant treatment—was adhered to in all the departments throughout the four-year period. During the off-treatment years thromboembolic complications were not treated with anticoagulants.

Other Treatment

The following fixed and uniform schedules were observed:

1. Strict rest in bed while the patient was ill (fever or pain), during which help was given with eating and washing. Thereafter he was allowed to use a commode, and to eat and wash without help.

2. After three weeks' rest in bed the patient was allowed to go to the lavatory.

3. At the end of another week (i.e., after at least four weeks) he was allowed out of bed.

4. Five weeks after admission to hospital the patient was discharged if no complications had arisen.

5. The medication for arrhythmias and congestive heart failure was uniform.

6. Prolonged and alarming shock was treated with noradrenaline.

7. Nitroglycerin was not given for two weeks after the acute episode.

8. Pain was treated with morphine.

The Patients

During the four years of the study the four departments admitted 1404 cases of acute myocardial infarction:

Total no. of patients	1404
Diagnosed post mortem	179 (*13%*)
Diagnosed >72 hours after onset	209 (*17%*)
Died during first 48 hours	216
No. of patients studied	800
Treated with anticoagulants	371
Without anticoagulants	429

In 179 cases (13%) the diagnosis was only made post mortem. This was a somewhat mixed group, mainly with a history of severe diseases—cerebrovascular accident, uræmia, cancer, &c. In 209 cases the diagnosis was not made until more than seventy-two hours after the onset of infarction, partly because of delayed admission to hospital and partly because of delayed diagnosis after admission. These were excluded because we thought the infarct was too old to be included in this study.

The patients proper thus totalled 1016. The effect of anticoagulant treatment, however, cannot be expected for forty-eight hours, and for this reason, we also excluded 216 patients who died within this time.

Thus there was a group of 371 patients treated with anticoagulants, and a group of 429 untreated—a total of 800. The two groups are not equal because, during the second half of our study the number of beds in one of the departments was cut by a third.

A condition for studying differences in the course of a disease within two groups must be that the groups are comparable. Ours were well-suited for comparison:

Sex ratio.—There was the well-known male preponderance, but no difference between treated and untreated patients:

	Treated	*Untreated*
Men	71%	64%
Women	29%	36%

Age distribution.—The average age was exactly the same in both groups. We also found, as is well known, that the women were about five years older than the men when they developed coronary thrombosis:

	Treated	*Untreated*
Men	64 years	63 years
Women	68 years	69 years

The *symptoms and signs* at admission showed excellent agreement between the two groups:

	Treated	*Untreated*
Acute typical pain	89%	84%
Acute pulmonary œdema	3%	4%
Acute pulmonary œdema and pain	4%	5%
Atypical start	4%	7%

The initial manifestation of the attack was predominantly the acute typical pain syndrome. This, as well as the more uncommon initial signs, was equally common in both groups.

The *E.C.G. findings* were also identical in the two groups. The classical types of infarction—anterior and posterior-wall—were found in three-quarters of all cases:

	Treated	*Untreated*
Anterior-wall infarction	40%	44%
Posterior-wall infarction	34%	34%
Bundle-branch block	6%	4%
Not classified	20%	18%

Factors influencing the outcome of acute myocardial infarction were:

	Treated	*Untreated*
Heart failure	22%	19%
Shock	10%	8%
Diabetes mellitus	9%	8·5%
Cardiac arrhythmia	28%	30%
Previous infarction	12%	14%
"Good" risk at 48 hours (Russek)	49%	49%
"Poor" risk at 48 hours (Russek)	51%	51%

Heart failure, shock, diabetes mellitus, arrhythmia, and previous myocardial infarction were equally distributed between the two groups. This was also true when the prognostic criteria of Russek (1951) were applied.

Thus, the two groups—anticoagulant-treated and non-anticoagulant-treated—were undoubtedly comparable, and differences in their subsequent course might reasonably be attributed to anticoagulants.

Intensity of Anticoagulant Treatment

No attempt was made to control the effect of the heparin therapy upon the clotting-time. The prothrombin-time was assessed by Owren's P & P method, and we tried to keep the patients in the so-called 10-25% therapeutic range:

The figure shows the length of time that the P & P value was below the 25% level. In 51% of cases it was below the 25% level for more than 90% of the treatment period. In 13%, the P & P value was below 25% for more than 80% of the treatment period. 17% were at this level for more than 70% of the time, and 19% of the cases were kept below the 25% level for less than 70% of the time. These results are not particularly impressive, but they are not inferior to those of previous workers. It is perhaps more important to establish that this is obtainable by dicoumarol therapy in departments where particular interest has been devoted to this form of treatment for several years.

Results

In assessing the possible effect of anticoagulants in acute myocardial infarction, three questions stand out:

1. Does the treatment influence the death-rate?
2. Does the treatment influence the frequence of thromboembolic complications?
3. What risks are involved in the treatment, with particular regard to fatal bleeding?

While the first question can be answered with certainty, the answers to the other two are less certain, because they involve differences in degree, which are not always so easy to evaluate.

Mortality

Acute myocardial infarction carries a very high mortality, and our series of 1016 patients is no exception. 410, giving an overall mortality-rate of 40%.

Table I shows the mortality in our two groups of treated and untreated patients after the first forty-eight hours. The figures were 23% and 25% in the treated and the untreated groups respectively—a difference which is not significant. We must conclude, therefore, that treatment with anticoagulants did not significantly alter the mortality from acute myocardial infarction in our series.

There was no difference in the mortality-rate for men within the different age-groups. This also applies to the younger women, but among elderly women the mortality-rate was somewhat higher in the untreated group, though the difference is not significant.

That patients classified as "poor risks" according to Russek's criteria (1951) show a higher mortality-rate is no cause for

TABLE I—MORTALITY IN 800 PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Sex and age	Anticoagulant treatment (371 patients)	No anticoagulant treatment (429 patients)
Men <65 yr.	20 of 145 (*14%*)	26 of 176 (*15%*)
Men >65 yr.	40 of 119 (*34%*)	33 of 100 (*33%*)
Total men	60 of 264 (*23%*)	59 of 276 (*21%*)
Women <65 yr.	7 of 43 (*16%*)	9 of 50 (*18%*)
Women >65 yr.	18 of 64 (*28%*)	41 of 103 (*40%*) (P=0·10)
Total women	25 of 107 (*23%*)	50 of 153 (*33%*) (P=0·10)
Total	85 of 371 (*23%*)	109 of 429 (*25%*) (P=0·40)

wonder, but it did not seem to make any difference whether or not the patients had had anticoagulants:

	Treated	*Untreated*
"Good risk"	9%	11%
"Poor risk"	37%	40%

Thromboembolic Complications

These were recorded partly as clinically demonstrable complications, and partly as postmortem findings, thus:

	Anticoagulants	*No anticoagulants*
Clinical thromboembolic manifestations	38 (*10%*)	58 (*14%*) (P = 0·20)
Thromboembolic manifestations found clinically and/or at necropsy	57 (*15%*)	108 (*25%*) (P = 0·01)

"Clinically demonstrable" thrombœmbolic complications included all cases of thrombophlebitis, pulmonary infarction, further myocardial infarctions, and emboli of the kidneys, brain, limbs, mesenteric vessels, &c. These were found in 10% of the anticoagulant-treated patients and in 14% of the untreated ones. This difference is slight and not significant.

As is well known, the clinical diagnosis of thrombosis and embolism is often uncertain. Since a large proportion of our patients died, and most of these were submitted to necropsy (90%), the clinical and postmortem findings can be analysed together. This confirms the inadequacy of clinical diagnosis, and shows that many more patients with thromboembolic complications were in the group not given anticoagulants; this difference is statistically significant.

TABLE II—PULMONARY AND CARDIAC THROMBOEMBOLIC MANIFESTATIONS IN ACUTE MYOCARDIAL INFARCTION: NECROPSY FINDINGS

Necropsy findings	Anticoagulant treatment (371 patients: 85 dead, 84 necropsies)	No anticoagulant treatment (429 patients: 109 dead, 92 necropsies)
Pulmonary infarction „ embolism „ thrombosis	4 of 84 or *5%* (*1%* of 371)	26 of 92 or *28%*: P = 0·01 (*6%* of 429)
Parietal thrombosis of the heart	20 of 84 or *24%*	53 of 92 or 58%: P = 0·01
Peripheral embolism in patients with parietal thrombosis	3 of 20 or *15%*	5 of 53 or *9%*
Mortality from thromboembolism	5 (*1·4%*)	17 (*4%*): P = 0·04

The number of thromboembolic complications found clinically and/or post mortem, classified by sex and age, were:

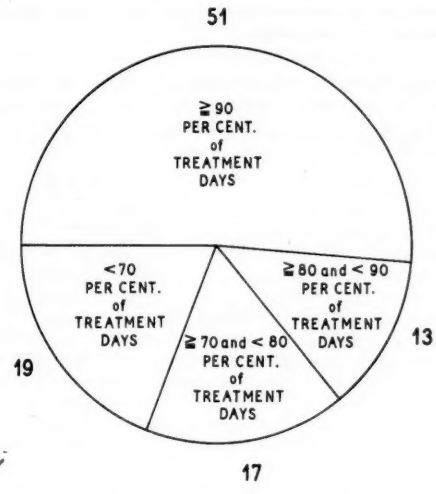
		Anticoagulants	*No anticoagulants*
Men	<65 years	9·7%	16·6%
	>65 years	17·8%	32·3%
Women	<65 years	18·6%	25·0%
	>65 years	22·2%	34·7%

It will be seen that the higher incidence of thromboembolic complications among the untreated cases is not due to an accumulation in any particular age or sex group.

While the clinical diagnosis of pulmonary infarction is often somewhat questionable, the postmortem finding of pulmonary embolism, infarction, and thrombosis is generally beyond dispute. Table II shows that this finding is appreciably commoner among untreated than among treated patients; in other words, anticoagulants considerably reduced the incidence of this complication.

TABLE III—TOTAL MORTALITY, AND MORTALITY FROM THROMBOEMBOLIC COMPLICATIONS, IN 800 CASES OF ACUTE MYOCARDIAL INFARCTION

Sex and age	Anticoagulant treatment (371 patients)		No anticoagulant treatment (429 patients)	
	Total mortality (%)	Died from thromboembolism	Total mortality (%)	Died from thromboembolism
Men <65 yr.	*14*	0	*15*	3
Men >65 yr.	*34*	2	*33*	7
Women <65 yr.	*16*	0	*18*	2
Women >65 yr.	*28*	3	*40*	5
Total	*23%*	5 (*1·4%*)	*25%*	17 (*4·0%*)


51
≥90 PER CENT. of TREATMENT DAYS
<70 PER CENT. of TREATMENT DAYS
≥80 and <90 PER CENT. of TREATMENT DAYS
≥70 and <80 PER CENT. of TREATMENT DAYS
19
13
17

Intensity of anticoagulant therapy.
Cases are grouped according to the proportion of days when the P & P values were below 25%.

But, as a cause of death, pulmonary embolism is not important.

Another common manifestation in acute myocardial infarction is mural thrombosis, and we found the incidence to be considerably lower among the anticoagulant-treated patients. Whether this affords any advantage is debatable. Mural thrombosis may be interpreted as a useful process of repair and protection. But, at the same time, it involves a risk of peripheral embolism. This risk materialised in only very few of our patients, and not particularly among the untreated ones (table II). Thus, anticoagulants may reduce the tendency to mural thrombosis, but we have not shown that this has any particular advantage.

An important question is how often the thromboembolic complications have been fatal. The difficulty of attributing death to one factor is obvious; but, as far as we could estimate, thromboembolic complications caused death in 5 cases of the treated group and in 17 of the untreated group (table II). Although the difference is significant, it counts for little in the total mortality of the two groups, and this did not show any definite difference.

We tried to decide whether the patients who died of thromboembolic complications could be assigned to any particular group. There was a decrease (which was not significant) in the mortality among treated as compared with untreated patients only in the women over 65. One might imagine, then, that the thromboembolic deaths were in this group, but table III shows that this was not so. The main preponderance of thromboembolic deaths was among men over 65—a group in which treated and untreated patients showed exactly the same mortality-rate.

If anticoagulant treatment reduces the risk of thromboembolism, as it does seem to do, fewer such complications would be expected in patients maintained for as long as possible at the "ideal" P & P level.

This is suggested by the finding of thromboembolic complications (clinical and postmortem) in 13% of the 51% of the patients whose P & P value had been kept at the best possible level (fig. 1). Among the other patients the incidence was 18%. But this difference is not statistically significant, and the advantage of keeping the P & P values below 25% is less evident considering that clinically demonstrable thromboembolic complications developed in 15 patients out of 32 when

the value had been below 25% on the day of the episode and for the four preceding days.

Risks of Anticoagulant Treatment

Allergic reactions seem to be extremely rare, but anticoagulants do cause an increased bleeding tendency. Bleeding episodes arose in the total series of 1016 patients as follows:

Treated with anticoagulants	81 of 426 cases (*19%*)
Without anticoagulants	11 of 530 cases (*2%*)

A fifth of the patients had major or minor bleeding, especially during long-continued therapy with dicoumarol.

The main types of bleeding were hæmaturia, epistaxis, and hæmoptysis. In most cases this was not important. A few cases were more serious, and 4 patients succumbed to hæmorrhage arising during anticoagulant medication—1 on the second day, and 3 later. Of these patients 2 developed melæna, and 1 of them also had hæmatemesis. Both required transfusions because of shock and anæmia, and then pulmonary œdema developed. 1 patient had a fatal hæmatemesis which proved to be due to œsophageal varices in non-diagnosed hepatic cirrhosis. Another died in shock because of a large subpleural hæmatoma.

It has often been stated (Waldron et al. 1954, Lee and O'Neal 1956, Capeci and Levy 1959) that the incidence of cardiac rupture is increased among patients having anticoagulants, but this was not confirmed in our series, which showed no difference:

	Anticoagulants (371 patients: 85 dead, 84 necropsies)	*No anticoagulants* (429 patients: 109 dead, 92 necropsies)
Cardiac rupture	7 of 84 (*8·3%*)	10 of 92 (*10·9%*)
Hæmorrhagic pericardial effusion (without rupture)	10 of 84 (*11·9%*)	4 of 92 (*4·3%*)

On the other hand, hæmorrhagic pericardial effusion without macroscopic rupture was three times more common among treated than untreated patients, but this was not recorded as the cause of death in more than one case of each group.

Discussion

We were unable to demonstrate a definite reduction in the mortality of acute myocardial infarction when treated with anticoagulants, or to show a definite decrease in clinically demonstrable thromboembolic complications. But, on the other hand, postmortem examination showed fewer thromboembolic incidents in treated than in untreated patients. This applies particularly to pulmonary infarction and pulmonary emboli, and to mural thromboses in the heart.

Analysis of the causes of death showed an unmistakable reduction in deaths from thromboembolic episodes in the treated cases. Compared with the total mortality, however, this is of very little significance.

Classification by sex and age revealed the same mortality-rate in untreated and treated male patients over and under 65, and in female patients under 65. In females over 65 there was a slightly (but not significantly) lower mortality among the treated patients. This suggested the possibility that most thromboembolic complications had been prevented among elderly women, but this did not prove to be so. The decrease in the thromboembolic manifestations found post mortem, and the decrease in deaths from this cause, were distributed more or less evenly in all groups.

The prophylactic effect of anticoagulant therapy must be weighed against its risks. Bleeding was recorded in about a fifth of the treated cases, and although this was mostly of no account, in several cases it was fairly severe, and 4 patients died of hæmorrhages. The treated group did not show an increased incidence of cardiac rupture, but hæmorrhagic pericardial effusion without rupture was considerably increased.

How should these negative results be interpreted against the background of so many previous favourable reports of anticoagulant treatment? In these thromboembolic complications seem to have been more common than in our series. From 1948-54 thromboembolic episodes were reported in 25-35% of untreated patients. In our series and in the series of Eastman et al. (1957) and Honey and Truelove (1957), the incidence was only 10-15%. It seems likely that the previous very strict regimen for treating acute myocardial infarction favoured thromboembolic complications, whereas these have been reduced by the greater mobilisation currently used. If only for this reason anticoagulants will be less effective in preventing thombotic complications.

Conclusion

From our studies we must conclude that anticoagulant therapy for acute myocardial infarction has some prophylactic effect against thromboembolism, but that quantitatively it is of little importance today. Against this, one must weigh the risks of the treatment. Overall, we could not demonstrate any reduction in the mortality-rate. Accordingly, we feel that anticoagulant treatment is not indicated in acute myocardial infarction. The prognosis of this disease seems to be largely determined by factors not influenced by anticoagulant therapy.

Summary

A controlled study of anticoagulant therapy in acute myocardial infarction was undertaken in four municipal departments of medicine in Copenhagen. In each department, anticoagulants were used for two out of four years; thus during each of the four years the treatment was used in two departments. At the same time, definite diagnostic criteria, and a common treatment schedule, were introduced.

During the experimental period 1404 cases of acute myocardial infarction were admitted to these departments. After excluding cases diagnosed only post mortem (179 patients), those diagnosed more than seventy-two hours after the onset of infarction (209 patients), and cases which died within the first forty-eight hours (216 patients), 800 cases were left. Of these 371 were treated with anticoagulants and 429 without. The two groups were comparable in every respect.

Anticoagulant therapy did not definitely reduce the number of clinically demonstrable thromboembolic complications; these occurred in 14% of the untreated cases and in 10% of the treated cases. On the other hand, fewer thromboses and emboli were found post mortem—especially pulmonary infarctions, pulmonary emboli, and cardiac mural thrombi. Moreover, the number of deaths from thromboembolic complications decreased unmistakably, though compared with the total mortality this was of little significance.

Against the value in preventing thromboses, one must weigh the risks of the treatment. 4 patients died from hæmorrhage. Cardiac rupture was equally common in both groups, but hæmorrhagic pericardial effusion without rupture was three times more common among the treated cases.

The overall result shows a total mortality of 25% in untreated and 23% in treated cases. This difference is not significant. The conclusion must be that anticoagulant therapy is not indicated in acute myocardial infarction.

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REFERENCES

Beckwith, J. R., Kernodle, D. T., Letten, A. E., Wood, J. E. (1954) *Ann. intern. Med.* **41**, 1189
Capeci, N. E., Levy, R. L. (1959) *Amer. J. Med.* **26**, 76.
Eastman, G. L., Cook, E. T., Shinn, E. T., Dutton, R. E., Lyons, R. H. (1957) *Amer. J. med. Sci.* **233**, 647.
Evans, W. (1954) *Proc. R. Soc. Med.* **47**, 318.
Feldman, L., O'Connor, W. R., Friedman, I. A., Fischer, J. W. (1952) *Amer. Heart J.* **44**, 112.
Garb, S. (1955) *Amer. J. med. Sci.* **229**, 534.
Glueck, H. I., Strauss, W., Pearson, J. S., McGuire, J. (1948) *Amer. Heart J.* **35**, 269.
Helander, S. (1958) *Acta med. scand.* **162**, 351.
Holten, C. (1951) *ibid.* **140**, 340.
Honey, G. E., Truelove, S. C. (1957) *Lancet*, i, 1155.
Lee, K. T., O'Neal, R. M. (1956) *Amer. J. Med.* **21**, 555.
Manchester, B., Ralkin, B. (1954) *Circulation*, **10**, 691.
Owren, P. A., Aas, K. (1951) *Scand. J. clin. Lab. Invest.* **3**, 201.
Russek, H. I., Zohman, B. L., White L. G., Doerner, A. A. (1951) *J. Amer. med. Ass.* **145**, 390.
Rytand, D. A. (1951) *Arch. intern. med.* **88**, 207.
Schilling, F. J. (1950) *J. Amer. med. Ass.* **143**, 785.
Schnur, S. (1953) *Circulation*, **7**, 855.
Tulloch, J. A., Gilchrist, A. R. (1950) *Brit. med. J.* ii, 965.
Waldron, B. R., Fennell, R. H., Castleman, B., Bland, E. F. (1954) *New Engl. J. Med.* **251**, 892.
Wright, I. S., Marple, C. D., Beck, D. F. (1948) *Amer. Heart J.* **36**, 801.
— — — (1954) Myocardial Infarction. New York.

HÆMODYNAMIC EFFECTS OF GUANETHIDINE

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GUANETHIDINE (' Ismelin ') is a drug that is becoming widely used to treat patients with severe hypertension. It probably lowers the blood-pressure by blocking post-ganglionic adrenergic neurones, and it does not produce symptoms of parasympathetic blockade. When the patient is supine his blood-pressure is usually little affected, but when he stands the blood-pressure is reduced: in this respect guanethidine resembles the ganglion-blocking drugs. Many patients taking guanethidine become even more hypotensive during exertion (Leishman et al. 1959, Dollery et al. 1960, Sturzenegger et al. 1960). This hypotension on effort can be severe enough to cause symptoms and even syncope, especially in the morning when the postural fall seems to be greatest. In a standing patient we have observed a fall in blood-pressure from 220/130 to 90/40 mm. Hg after climbing two flights of stairs. This effect is one of the practical problems that guanethidine poses to the clinician, particularly in the treatment of hypertensive patients with ischæmia of the heart or brain.

Bretylium tosylate also causes hypotension on effort (Lowe and Rosenheim 1960, Turner and Lowther 1960), and the fall in blood-pressure is of the same order as that caused by guanethidine. Taylor and Donald (1960) have shown that, during exertion in patients taking bretylium, the fall in blood-pressure is accompanied by a rise in cardiac output of the same degree as that produced by equal exertion without bretylium; and it appears that the fall in blood-pressure is brought about by a large reduction of peripheral resistance.

If guanethidine is injected intravenously, it usually causes an intense flush accompanied by a short-lived rise in blood-pressure. A similar transient increase of pressure also occurs after intravenous injections of bretylium (Taylor and Donald 1960), but not after ganglion-blocking drugs.

We have studied the hypotension, on standing and during exertion, caused by guanethidine taken orally, by comparing the cardiac output and blood-pressure before and after exercise and changes of posture. We have also studied the hypertension that follows intravenous injection of guanethidine. These tests have led to a better understanding of the anomalous action of guanethidine during exercise, and of its use in the treatment of severe hypertension.

Investigation

The Patients

We studied thirteen patients, all of whom had severe hypertension, and who had been selected for long-continued treatment with guanethidine. Ten patients were already being treated orally with guanethidine at the time of the investigation, and most of these were known to have a fall of blood-pressure on effort. Of these, cases 11 and 12 were given an additional 20–40 mg. of guanethidine intravenously during the study. Three others (cases 1, 9, and 10) were given their first dose (20–40 mg.) of guanethidine intravenously during the investigation. The indications for treatment of the hypertensive disease in these thirteen patients were:

Condition	*Case nos.*
Malignant hypertension	2, 3, and 13
Hypertension with retinal hæmorrhages and exudates	1, 4, 5, 8, and 10–12
Severe hypertension without exudative retinopathy	6, 7, and 9

Methods

Serial estimations of the changes in cardiac output were made by a dye-dilution method. Coomassie blue was injected into the right atrium through a catheter in an arm vein in twelve of the thirteen patients; in the other patient the injections were made into a peripheral vein. The dye curves were recorded from an ear oximeter, and equal doses of dye were injected at intervals (Gabe and Shillingford 1961). The earpiece and cuvette recorder systems were arranged to give a linear response to the dye over the range of concentrations used. In this way changes in the cardiac output can be estimated by comparing the reciprocals of the areas enclosed by the curves when plotted semilogarithmically (Lee 1960). Absolute values of cardiac output were not calculated, but the changes were related to basal cardiac output recorded before exercise or tilting, and expressed as percentages.

It was assumed that the sensitivity of the earpiece did not change under the various experimental conditions. This was tested in two patients by comparing the ear-oximeter curves with curves simultaneously recorded from an arterial cuvette. These curves proved to be closely similar except when patients tilted feet down felt faint from a very great fall in blood-pressure. When this happened the area of the curve recorded from the earpiece was less than that from the arterial cuvette, and so the estimate of cardiac output from the earpiece was too high. As syncope approaches blood drains from the ear and the recorded curves are modified. Guanethidine was given intravenously soon after the resting cardiac outputs were measured, with exercise or with tilting in random order. Blood-pressure was recorded from the brachial artery with a standard sphygmomanometer.

During the exercise test patients lay flat and pedalled a bicycle ergometer. The amount of work varied because we stopped the exercise as soon as they became breathless. The exercise lasted for 3–5 minutes. Similarly, the degree and duration of tilting also varied; if the blood-pressure fell very low patients were laid flat at once.

Results

Table I contains the values of dye appearance-time, blood-pressure, and the percentage change in cardiac output, in all thirteen patients at rest, on tilting, and on exercise. The lowest value of resting cardiac output was

TABLE I—CHANGE IN CARDIAC OUTPUT (C.O.) DYE APPEARANCE-TIME (A.T.) AND BRACHIAL BLOOD-PRESSURE (B.P.) IN 13 PATIENTS TREATED WITH GUANETHIDINE

Case no.	Rest		Tilting with feet down			Exercise		
	A.T. (sec.)	B.P. (mm. Hg)	A.T. (sec.)	B.P. (mm. Hg)	Change in C.O. (%)	A.T. (sec.)	B.P. (mm. Hg)	Change in C.O. (%)
1*	9	240/135	16	170/110	−54	..	..	..
2	7·5	280/155	5·5	270/155	+1	7·5	210/130	+127
3	8·5	220/105	8·5	225/100	−17	8·5	235/110	+13
4	8	200/110	9	120/85	−31	7	210/110	+15
5	5·5	215/120	6·5	190/100	−20	5·5	180/70	+33
6	6·3	235/110	6·5	195/105	−4	5·5	190/90	+82
7	11	190/115	11	195/120	+10	10	210/130	+31
8	13	230/135	13	230/120	+16	10	190/120	+215
9	8·5	180/100	11	110/85	−14	9·5	140/80	−22
10	9	155/105	10·5	80/60	−21	6·2	160/110	+13
11	8	205/120	12·5	100/70	−26	8·5	160/80	+87
12	8	250/150	..	..	..	7	180/80	+78
13*	8·5	215/120	..	..	..	6	140/70	+96

* The changes in cardiac output were calculated from arterial-cuvette curves

regarded as 100%, and where more than one reading was made on exercise or on tilting the measurements at the lowest blood-pressure were tabulated.

Effect of Tilting

Measurements of blood-pressure and cardiac output were made in eleven patients before and after tilting with the feet down. The angle of tilt varied between 30° and 65°. In seven of the eleven patients the blood-pressure fell on tilting, and the cardiac output fell in each. The fall in cardiac output was usually only moderate—between 4 and 54%, with a mean of 24%. In some patients who had a substantial fall in blood-pressure the extent of the fall in cardiac output was probably underestimated by the ear-oximeter method. The appearance-time of the dye at the ear was prolonged in two patients (nos. 10 and 11), who had a substantial fall in blood-pressure but only a moderate change in output, as calculated from the ear-oximeter curve.

The ear-oximeter and arterial-cuvette curves of case 1, whose pressure fell from 240/135 to 170/110 mm. Hg when tilted with the feet down, and whose output fell by 54%, are shown in figs. 1 and 2.

Effect of Exercise

Measurements were made from twelve patients before and immediately after exercise. Because, during exercise, it was not possible to achieve a stable baseline from the earpiece, the injection of dye was made within 10 seconds of stopping exercise. The blood-pressure fell during exertion in eight of the twelve patients, and in all save one this fall was associated with a rise in cardiac output. The change in output of the seven in whom it rose varied between +33 and +215%, with a mean of +102%. There was a moderate fall in the blood-pressure of most patients, but in three (cases 5, 12, and 13) it was large (215/120–180/70, 260/150–180/80, and 225/120–140/70 mm. Hg). Output curves from case 13 are shown in fig. 3.

We have previously observed (Dollery et al. 1960) that the fall of blood-pressure on effort is followed by a "rebound", during which the pressure may slightly exceed that recorded

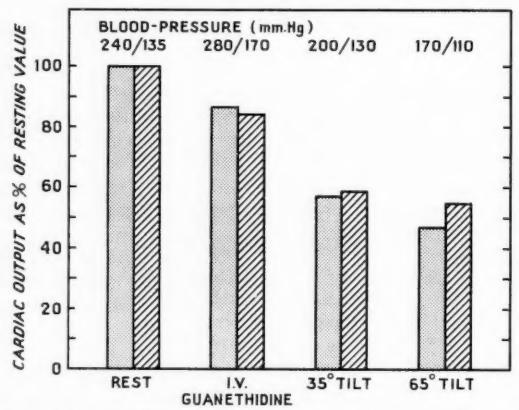

Fig. 2—Histogram showing the changes in cardiac output in case 1, measured with the arterial cuvette (shaded) and with the earpiece (hatched), compared with the changes in blood-pressure.

before the exertion. During the present investigation we measured the cardiac output and blood-pressure during the rebound phase in five patients within 3 minutes of stopping exertion (table II). On four of the five occasions the blood-pressure rose to the resting value or slightly higher before the cardiac output returned to its resting value.

"Acute" Effect of Guanethidine Intravenously

Guanethidine was given intravenously to five patients. Three of these (nos. 1, 9, and 10) had their first therapeutic dose in this way, and two others (nos. 11 and 12) who were already having guanethidine by mouth, were given an extra intravenous dose during the investigation. The cardiac outputs and blood-pressure of two patients were recorded during the pressor phase immediately after the injection. An example is shown in fig. 1. The blood-pressure rose in both patients; the cardiac output rose slightly in one and fell slightly in the other (table III).

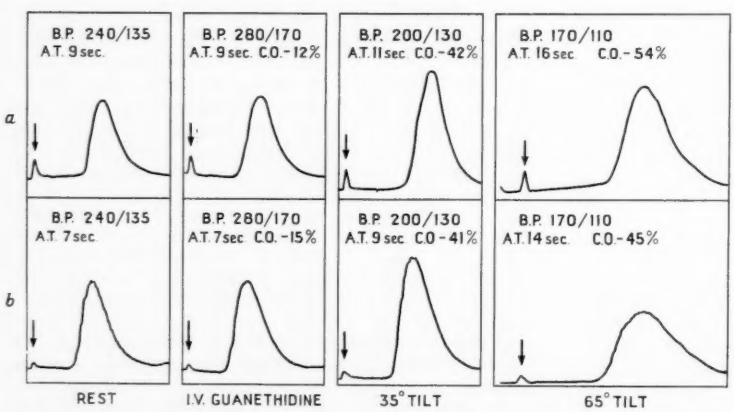

Fig. 1—Dye curve from case 1, recorded from *(a)* arterial cuvette, and *(b)* ear oximeter.
The blood-pressure, appearance-time, and relative cardiac output are shown under basal conditions at rest, during the pressor phase after guanethidine intravenously, and at two different angles of tilt.

The curves show very good agreement except at 65° of tilt, when, despite a blood-pressure of 170/110, the patient became pale and felt faint. In these curves the appearance-time (A.T.) was prolonged, and the cardiac output (C.O.) calculated from the cuvette curves was lower than that from the earpiece curves. (The cardiac output is inversely proportional to the area under the curves.)

Discussion

The therapeutically important effect of guanethidine is the reduction of blood-pressure when the patient stands. Our results show that in these circumstances the acute fall of pressure is associated with a moderate to severe fall in cardiac output. This effect of guanethidine resembles that of the ganglion-blocking drugs (Hoobler et al. 1955). Previous results with guanethidine have been conflicting: Richardson et al. (1960) found a fall in cardiac output, but Lichtler et al.

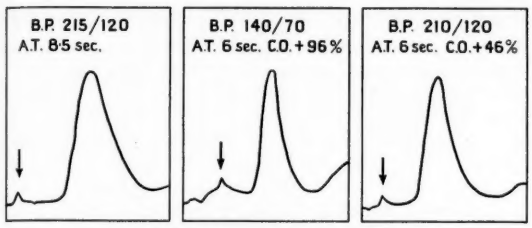

Fig. 3—The effect of 3 minutes' leg exercise in case 13.
The cardiac output increased by 96%, and the blood-pressure fell from 215/120 to 140/70 mm. Hg. 3 minutes after stopping exercise (last tracing) the blood-pressure had returned to 210/120, but the cardiac output was still 46% above the resting value.

(1960) found that cardiac output stayed fairly constant, and they attributed the fall in blood-pressure to a lessening of peripheral resistance. To some extent the distinction is theoretical. Normally the cardiac output falls on standing and the blood-pressure is maintained by an increase in peripheral resistance. But, because patients treated with guanethidine apparently cannot produce vasoconstriction when they are titled with the feet downwards, the fall in cardiac output causes a fall in blood-pressure. For example, the cardiac output of case 1 fell to less than half the resting value. This change, probably provoked by the failure of peripheral vasoconstriction with consequent venous pooling, caused a striking fall in blood-pressure. Changes in the total peripheral resistance

TABLE II—CARDIAC OUTPUT, APPEARANCE-TIME, AND BLOOD-PRESSURE IN PATIENTS STUDIED DURING RECOVERY FROM EXERCISE

Case no.	Rest		Exercise			Recovery from exercise		
	A.T. (sec.)	B.P. (mm. Hg)	A.T. (sec.)	B.P. (mm. Hg)	Change in C.O. (%)	A.T. (sec.)	B.P. (mm. Hg)	Change in C.O. (%)
2	7·5	280/155	7·5	210/130	+127	7·3	280/160	+42
3	8·5	220/105	8·5	225/100	+13	8·5	235/110	−10
6	6·2	235/110	5·5	190/90	+82	5·2	250/120	+62
12	8	260/150	7	180/80	+18	8	270/150	+21
13	8·5	215/120	6	140/70	+96	6	210/120	+46

(calculated from the mean pressure and change in output) on tilting were inconstant. In most patients the resistance fell, but in two it rose.

The hypotension on effort experienced by many patients treated with guanethidine is of considerable practical importance. A similar effect was first observed with bretylium tosylate; Lowe and Rosenheim (1960) suggested that it might happen because the cardiac output failed to rise on effort, but Taylor and Donald (1960) showed that the response of the cardiac output to exertion was normal. Taylor and Donald also studied the effect of guanethidine given intravenously in five patients, but they did not find a significant change in blood-pressure on exertion. We are uncertain why our results differ from theirs. A possible explanation is that the circulatory effects of guanethidine given by " acute " intravenous injection

TABLE III—CARDIAC OUTPUT, APPEARANCE-TIME, AND BLOOD-PRESSURE 1 MINUTE AFTER GUANETHIDINE INTRAVENOUSLY

Case no.	Rest		After guanethidine I.V.		
	A.T. (sec.)	B.P. (mm. Hg)	A.T. (sec.)	B.P. (mm. Hg)	Change in C.O. (%)
1	9	240/135	9	280/170	−12
10	9	155/105	6·7	210/120	+27

differ from those caused by long-continued treatment by mouth. Two of our patients were exercised after intravenous doses of guanethidine: both showed a striking fall in blood-pressure when they were tilted, but neither had a fall in pressure on exercise. In case 9, the blood-pressure fell on tilting and did not return to the initial value recorded before exercise. In some instances patients who had guanethidine by mouth showed a greater fall on exercise than on tilting. The distinction is clearly not absolute, but it may partly explain a puzzling discrepancy.

The rapid rebound in blood-pressure within 1–3 minutes of stopping exercise happens when the cardiac output is still raised. Guanethidine seems to interfere with the rapid matching of peripheral resistance to cardiac output that normally takes place during and after exercise. As the cardiac output increases during exercise and the blood-pressure falls, the peripheral resistance is greatly reduced. Because the peripheral resistance normally falls during exertion the blood-pressure remains more or less constant, but this fall in resistance is much exaggerated in some hypertensive patients treated with guanethidine.

The hypertensive phase after intravenous doses of guanethidine appeared to be entirely caused by peripheral vasoconstriction as the cardiac output was little changed. The blood-pressure rose while the skin was flushed and the cardiac output was stable. This suggests that the vasoconstriction was predominantly in the muscular or visceral circulations. The pressor action is important because the blood-pressure may rise to worrying levels in patients who are already severely hypertensive. For this reason we do not think guanethidine should be given intravenously in routine clinical practice. If urgent reduction of blood-pressure is needed, injections of ganglion-blocking drugs are preferable because they have no pressor action.

While our results throw some light on the hæmodynamic response of the hypertensive patient to guanethidine orally and parenterally, they do not indicate any way of preventing the hypotension on exercise. Further study of this problem will involve detailed measurements of the effects of guanethidine on the peripheral circulation.

It is worth emphasising how troublesome exercise hypotension can be to some patients, particularly those who do heavy work or who have to climb many flights of stairs. Since the cardiac output increases in response to exercise in a normal fashion, the effect will usually only reduce tissue blood-flow when the blood-pressure falls to below normal values. Particular attention must be paid to this problem when treating patients with ischæmia of the heart or brain, in whom falls of blood-pressure may reduce tissue perfusion and induce alarming symptoms.

Summary

The hæmodynamic response to guanethidine has been studied in thirteen severely hypertensive patients.

Seven of eleven patients showed a fall in blood-pressure when they were tilted feet down, and in them the cardiac output fell by a mean of 24%.

On exercise eight of twelve patients showed a fall in blood-pressure, and in seven of these the cardiac output rose with exertion. In five patients further cardiac output measurements were made during recovery from exertion: the blood-pressure rebounded to its previous value or higher, while in four of them the cardiac output was still above the resting value.

Measurements made shortly after intravenous injections of guanethidine showed that the blood-pressure rose, with little change in cardiac output.

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REFERENCES

Dollery, C. T., Emslie-Smith, D., Milne, M. D. (1960) *Lancet*, ii, 381.
Gabe, I. T., Shillingford, J. P. (1961) *Brit. Heart J.* **23**, 271.
Hoobler, S., Cottier, P., Weller, J., Smith, J. (1955) *J. Lab. clin. Med.* **46**, 828.
Lee, G. de J. (1960) *in* Clinical Disorders of the Pulmonary Circulation (edited by R. Daley, J. F. Goodwin, and R. E. Steiner); p. 21. London.
Leishman, A. W. D., Matthews, H. L., Smith, A. J. (1959) *Lancet*, ii, 1044.
Lichtler, P., Schaub, F., Bühlmann, A. (1960) *Dtsch. med. Wschr.* **85**, 1249.
Lowe, R. D., Rosenheim, M. L. (1960) *Lancet*, i, 655.
Sturzenegger, E., Sieganthaler, W., Lüthy, E. (1960) *Dtsch. med. Wschr.* **85**, 1229.
Taylor, S. H., Donald, K. W. (1960) *Lancet*. ii, 389.
Turner, R., Lowther, C. (1960) *ibid.* i, 769.
Richardson, D. W., Wyso, E. M., Magee, J. H., Cavell, G. C. (1960) *Circulation*, **22**, 184.

GUANETHIDINE AND HYDROCHLOROTHIAZIDE IN THE TREATMENT OF HYPERTENSION

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THE introduction of guanethidine for the treatment of hypertension has marked a real advance in the management of this condition. Guanethidine is effective as a blood-pressure lowering agent, can be given in a single morning dose, does not appear to produce resistance and has fewer troublesome side-effects than ganglion-blocking agents. The use of guanethidine in combination with one of the thiazide group of diuretics extends the application of these drugs in the management of patients with high blood-pressure. We have compared the efficacy of a combination of guanethidine and hydrochlorothiazide with the results obtained with guanethidine alone. The addition of hydrochlorothiazide appears to reduce the quantity of guanethidine required to control the blood-pressure.

Material and Methods

The patients were attending or had been referred to the clinic for hypertensive patients at the Central Middlesex Hospital. The general measures of weight reduction, modification of the way of life, and salt restriction had, where indicated, been carried out. The more severe cases were treated in hospital whilst changing to or being stabilised on guanethidine; others were seen at the weekly afternoon clinic.

An attempt was made to assess the severity of the hypertension in each patient by the level of the blood-pressure before treatment, and by the presence of left ventricular hypertrophy electrocardiographically and radiologically, the presence of retinal hæmorrhages and exudates, and albuminuria. Patients were advised to take guanethidine in a single morning dose, and the dose was generally increased at weekly intervals until a satisfactory level of blood-pressure was achieved (160/100 mm. Hg or below with the patient standing).

TABLE I—AGE DISTRIBUTION OF 65 TREATED PATIENTS

Age (yr.)	No. of patients
40–44	5
45–49	9
50–54	14
55–59	20
60+	17

TABLE II—GRADING OF THE SEVERITY OF HYPERTENSION IN 65 TREATED PATIENTS

Diastolic blood-pressure (mm. Hg)	No. of patients
100–109	1
110–119	5
120–129	14
130–139	18
140–149	14
150–159	12
160+	1

The effect of combining the administration of guanethidine with hydrochlorothiazide was investigated using an enteric-coated tablet * containing guanethidine 10 mg. hydrochlorothiazide 10 mg., and potassium chloride 600 mg. The number of combined tablets required to produce the same degree of lowering of blood-pressure as guanethidine (10 mg.) tablets alone was determined in 22 patients in whom the blood-pressure was satisfactorily controlled by guanethidine alone. Blood-urea and serum-potassium levels were determined before and during treatment with the combined tablet.

Results

The 65 patients treated included 41 males and 24 females. The age distribution is shown in table I. The hypertension was regarded as essential in 47, malignant in 8, due to previous renal disease in 6, and following toxæmia of pregnancy in 4. Some indication of the severity of the hypertension is given by table II, where the patients are grouped according to the level of diastolic blood-pressure before treatment. Left ventricular hypertrophy was present in 48 patients, retinopathy in 15, and albuminuria in 16.

The overall results in table III show that 57 patients had a satisfactory lowering of blood-pressure; 12 were receiving chlorothiazide in addition to guanethidine. Failure to respond was seen in 8 patients, including 5 with malignant hypertension. Of these 8 patients, 2 had intolerable looseness of the bowels, and 2 were troubled by nocturnal breathlessness which cleared when the guanethidine was stopped. A Polish man was unable to tolerate the inability to ejaculate. A woman with a cystocele awaiting surgery found her stress incontinence very much worse, and another woman suffered a minor cerebral hæmorrhage shortly after starting guanethidine. A Jamaican was slow to respond to guanethidine and was admitted to hospital and stabilised on pempidine and chlorothiazide.

TABLE III—RESULTS OF TREATMENT WITH GUANETHIDINE IN 65 CASES

Result	No. of cases
Response:	
Without side-effects	45
With side-effects	12
Failure	8

9 of the 45 responding without side-effects and 3 of the 12 with side-effects were also having chlorothiazide.

Side-effects were observed in 12 patients who responded satisfactorily. Some patients experienced more than one manifestation, but none were so severe as to interfere with continuing guanethidine. Looseness of bowels was observed 7 times; dizziness, giddiness, or unsteadiness 5 times, impairment of ejaculation 3 times, parotid pain twice, and bradycardia once.

A group of 22 patients (15 male, 7 female) controlled by guanethidine alone were treated with the combined tablet. 18 had essential hypertension, 2 had malignant hypertension, and 2 renal hypertension. Left ventricular hyper-

* Kindly supplied by Ciba Laboratories Ltd.

trophy was present in 16, retinopathy in 5, and albuminuria in 4. Treatment with guanethidine alone lowered blood-pressure satisfactorily in all cases; in 2 instances diastolic levels of 105 mm. Hg preceded the change to the combined tablet. When satisfactory control was achieved with guanethidine alone the patients were changed to the combined tablet of guanethidine, hydrochlorothiazide, and potassium chloride (table IV). In 20 patients the dose of guanethidine needed in the combined tablet was less than the dose of guanethidine alone; 2 patients (cases 19 and 22) required the same dose of guanethidine under both regimens. Case 7 was taking 220 mg. guanethidine; she was changed to 50 mg. guanethidine (five combined tablets) and was maintained on 100 mg. guanethidine. We felt that a larger dose of hydrochlorothiazide should be avoided in view of the possibility of potassium depletion. Serum-potassium and blood-urea estimations were made in the majority of patients before and during treatment with the combined tablet (table IV); serum-potassium levels were found to be lower than before in 5 of 11 paired observations by increments of 1·0, 0·9, 0·7, 0·5, and 0·5 mEq per litre. The blood-urea rose in 6 of 16 paired observations; the increases were 19, 7, 3, 2, and in 2 patients, 1 mg. per 100 ml. In the remaining 10 pairs it remained unaltered or fell. Whilst there was some reduction in the incidence of side-effects in 6 patients (table V) 7 of 16 who were free of side-effects on guanethidine alone developed side-effects on the combined tablet—looseness of the bowels in 3, abdominal pain in 4, dizziness in 3, and nocturia in 1.

Discussion

Guanethidine is an effective agent for lowering elevated blood-pressure when given as a single morning dose. The peak effect after a single morning dose and the duration of action are somewhat variable. Our patients were seen during the afternoon, six to ten hours after taking their guanethidine, when its effect might be waning. Satisfactory control of blood-pressure without side-effects in 45 (69%) patients compares favourably with the figures in other published series. Dollery et al. (1960) treated 80 patients and observed good control in 42·5%. Leishman et al. (1959) found that control was satisfactory in 13 out of 19 patients, whilst Evanson and Sears (1960) found that 16 of 17 patients responded satisfactorily to treatment as inpatients; outpatient follow up showed persistent satisfactory response in 10 out of 16 patients discharged on guanethidine.

TABLE IV—BLOOD-PRESSURE REDUCTION BY GUANETHIDINE AND BY EQUIVALENT DOSE OF GUANETHIDINE COMBINED WITH HYDROCHLOROTHIAZIDE AND POTASSIUM CHLORIDE

Case no.	Blood-pressure (mm. Hg)			No. of tablets		Serum-potassium (mEq./l.)		Blood-urea (mg. per 100 ml.)	
	A	B	C	a	b	Before	During	Before	During
1	220/120	150/80	140/85	3	2	4·5	..	36	..
2	210/120	185/95	210/105	12	6	..	..	..	..
3	260/140	210/105	160/90	8	5	3·8	5·4	27	27
4	220/120	230/100	180/100	7	4	..	4·8	41	41
5	260/140	170/100	180/100	4	3	4·9	4·4	44	41
6	270/170	110/70	140/95	7	6	4·0	4·6	51	35
7	260/125	190/90	160/95	22	5 (+10)	4·3	3·4	42	28
8	190/120	170/90	140/95	4	2	..	4·0	53	56
9	250/145	180/95	170/110	7	4	5·3	5·3	43	44
10	270/155	150/90	150/90	3	2	4·5	4·4	41	42
11	190/125	140/95	130/90	7	4	4·5	4·5	58	65
12	170/120	170/100	150/95	8	4	5·0	5·8	59	34
13	230/130	160/90	135/90	6	3	3·8	3·1	49	39
14	200/120	160/90	160/90	3	2	..	5·1	..	46
15	210/130	180/95	160/100	4	3	..	3·8	38	38
16	230/130	150/90	150/90	5	4	..	4·0	..	55
17	220/140	180/100	190/110	5	4	5·0	4·0	44	63
18	230/130	170/100	160/95	7	4	4·3	3·8	24	26
19	240/140	160/90	150/95	4	4	..	4·3	64	39
20	200/130	160/95	175/110	4	3	5·0	..	35	..
21	240/145	165/100	170/110	4	3	..	..	40	..
22	220/120	210/105	220/110	3	3	..	4·5	39	39

Note that use of the combined tablet lessened the quantity of guanethidine required.

Blood-pressure readings: A, before treatment; B, controlled by guanethidine; C, controlled by the combined tablet. Number of tablets: a, guanethidine 10 mg.; b, combined tablet containing guanethidine 10 mg., hydrochlorothiazide 10 mg., and potassium chloride 600 mg. Serum-potassium and blood-urea were estimated before and during treatment with the combined tablet.

TABLE V—REDUCTION IN FREQUENCY OF SIDE-EFFECTS OF GUANETHIDINE WHEN REPLACED BY GUANETHIDINE IN COMBINATION WITH HYDROCHLOROTHIAZIDE, IN 6 HYPERTENSIVE PATIENTS

Side-effect	Guanethidine alone	Guanethidine combination
Looseness of bowels	3	1
Dizziness	2	1
Impaired ejaculation	2	1
Leg weakness	1	1
Parotid pain	1	0
Bradycardia	1	1

The side-effects of treatment with guanethidine were similar to those observed by other workers. Looseness of the bowels, especially in the morning, often improved when morning tea was given up. When it persisted, propantheline bromide was helpful in its control. Although dizziness and muscular aching was a common side-effect, syncope after exercise was not observed. Taylor and Donald (1960) did not observe hypotension on exercise after guanethidine, as was observed with bretylium.

Tolerance to guanethidine was not observed in this group of patients or in those described by Dollery et al. (1960). Leishman et al. (1959) and Hilden (1960) have reported the development of tolerance.

Thiazide diuretics have been shown to have a blood-pressure-lowering effect (Bartorelli 1960, Freis 1960, McQueen and Morrison 1960, Smirk et al. 1960), and it has been suggested that combination of guanethidine with a diuretic is beneficial (Hilden 1960, Jaquerod and Spühler 1960). Among the 65 patients treated, 12 of the 57 who responded with a satisfactory lowering of blood-pressure were having chlorothiazide in addition to guanethidine. The results obtained with the combined tablet (table IV) indicate that combination of guanethidine with hydrochlorothiazide will generally reduce the quantity of guanethidine needed to maintain satisfactory blood-pressure control. Whilst changing to the combined tablet was associated with a reduction in the side-effects in 6 patients (table V) 7 patients developed side-effects on the combined tablet when they had been free of such manifestations on guanethidine alone. Hilden (1960) noted water retention in 4 out of 22 patients treated with guanethidine. This may have been the mechanism in 2 of our failures. This possibility emphasises one of the advantages of using guanethidine in combination with a diuretic which, in itself, has a blood-pressure-lowering action. One or two patients occasionally noticed remnants of the combined tablet in the stools. Toxic effects of hydrochlorothiazide therapy were absent; 1 patient was troubled by nocturia, but no symptoms of hypokalæmia were observed. Case 13 had a serum-potassium level of 3·8, falling to 3·1 mEq. per litre. We were interested in any effect guanethidine in combination might have on renal function. There was no clinical evidence of deterioration when guanethidine and hydrochlorothiazide were administered together. Richardson et al. (1960) found a reduction in glomerular-filtration rate and effective renal plasma-flow in 7 patients having oral guanethidine. Mertz (1960) also observed a transiently decreased renal

blood-flow, glomerular filtration-rate, urine volume, and output of solute. The rise in blood-urea levels of 19 and 7 mg. per 100 ml. in cases 11 and 17 could reflect a decreased glomerular filtration-rate—the minimal rise in 4 other patients is probably not significant.

Summary

Guanethidine lowered the blood-pressure satisfactorily in 57 of 65 hypertensive patients; 45 of these patients responded without side-effects. A combination of guanethidine and hydrochlorothiazide, administered to 22 patients, reduced the amount of guanethidine necessary to control the elevated blood-pressure in 20. A thiazide type of diuretic can, with advantage, be used in conjunction with guanethidine.

REFERENCES

Bartorelli, C. (1960) *in* Essential Hypertension (edited by K. D. Bock and P. T. Cottier); p. 283. Berlin.
Dollery, C. T., Emslie-Smith, D., Milne, M. D. (1960) *Lancet*, ii, 381.
Evanson, J. M., Sears, H. T. N. (1960) *ibid.* ii, 387.
Freis, E. D. (1960) *in* Essential Hypertension (edited by K. D. Bock and P. T. Cottier); p. 179. Berlin.
Hilden, T. (1960) *ibid.* p. 261.
Jaquerod, R., Spühler, O. (1960) *Schweiz. med. Wschr.* **90**, 113.
Leishman, A. W. D., Matthews, H. L., Smith, A. J. (1959) *Lancet*, ii, 1044.
McQueen, E. G., Morrison, R. B. I. (1950) *ibid.* i, 1209.
Mertz, D. P. (1960) *German med. Monthly*, **5**, 378.
Richardson, D. W., Wyso, E. M., Maguand, J. H., Cavell, G. C. (1960) *Circulation*, **22**, 184.
Smirk, H., McQueen, E. G., Morrison, R. B. I. (1960) *Brit. med. J.* i, 515.
Taylor, S. H., Donald, K. W. (1960) *Lancet*, ii, 389.

CALCIUM INTAKE IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

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THE dietary intake of calcium in patients who have developed primary hyperparathyroidism is of interest for two main reasons. In the first place a low intake of calcium may well be of ætiological significance since it might be expected to produce hyperplasia of the parathyroid glands. This situation is easily produced experimentally, and such hyperplasia, if sufficiently prolonged, could well result in one or more of the glands becoming adenomatous. The second point of interest lies in the fact that primary hyperparathyroidism occurs in two main clinical types—that without and that with bone disease (osteitis fibrosa generalisata). These two types are not related to differences in the pathology of the parathyroid tumour in question nor to differences in plasma calcium and phosphorus levels. It has been suggested that a major factor in directing the course of the disease to one or other type was the patient's previous calcium intake, a low intake predisposing to negative calcium balance and to osteitis fibrosa, a high intake inducing a positive balance and thus preventing this complication. Both these points of view were well argued by Albright and Reifenstein (1948) in their classic work on the parathyroid glands, to which reference should be made for further details.

In this paper we report the result of a dietary survey of previous intakes of calcium in patients with primary hyperparathyroidism. Phosphorus intakes are also recorded. In spite of the considerable theoretical and practical implications we are unaware of any previous report along these lines. This is especially surprising since ordinary clinical experience has often run at variance with the suggestion that previous calcium intake was of ætiological or other interest in primary hyperparathyroidism.

Methods

At the time of writing (December, 1960), 65 patients with primary hyperparathyroidism have been successfully operated on at University College Hospital, almost all of them by Mr. D. R. Davies. A preliminary report of the first 40 of these has already appeared (Dent 1959, Davies 1959). When the present survey was envisaged we wrote to as many as possible of the patients who had been operated on, to inquire into their dietary histories; and from then on we obtained details from all further cases. In this way we obtained 50 dietary histories. We have also added 1 further case with classical signs of primary hyperparathyroidism in which no parathyroid tumour was found in one operation at U.C.H. and in two previous ones elsewhere. Some of the patients manifested more complex syndromes of which the primary hyperparathyroidism comprised only a part. These are singled out for special description in the accompanying figures in case they should unfairly bias the results. The differentiation of each patient into the " with " or " without " bone disease group presented no particular problem. Those " with " bone disease all had plasma-alkaline-phosphatase levels of over 16 King-Armstrong (K.A.) units and showed the usual specific radiological bone changes. Those " without " bone disease had phosphatase levels below 14 K.A. units and showed no hyperparathyroid bone changes.

The average daily intake of calcium and phosphorus was estimated, using dietary tables (McCance and Widdowson 1946), by either a questionary sent to the patients operated on before 1958, when we began this study, or by direct questioning of the patient whilst in hospital. Each patient was asked to submit quantities and values of average food intake for a period of five years before the parathyroidectomy operation. When the patients were questioned especial importance was attached to the quantities taken of the calcium-rich and phosphorus-rich foods—namely, for calcium: milk, cheese, eggs, bony fish, bread, and green vegetables; and for phosphorus: liver and red meats. We also inquired particularly as to the water content of the diet in relation to the variation between hard and soft water areas in this country. Specific diet and medicinal therapy given during the period were also taken into account.

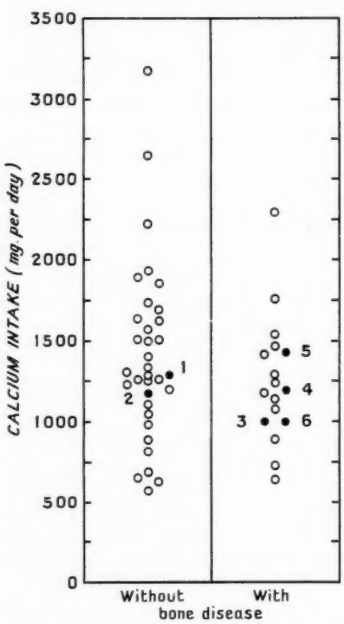

Fig. 1—Preoperative calcium intakes of patients with primary hyperparathyroidism.

The patients were all straightforward examples of the disease with or without bone disease, except for the 6 indicated by black circles.

Results

These results

are shown in figs. 1 and 2, which are self-explanatory.

The patients with unusual features (black circles in figs. 1 and 2) were as follows:

(1) This patient also had typical idiopathic osteoporosis not affected by removal of the parathyroid tumour.

(2) This patient had acromegaly. Signs of hyperinsulinism were sought but not found.

(3) This patient was case 2 of Davies, Dent, and Willcox (1956). Two parathyroid tumours were believed to have grown on the basis of lifelong cœliac disease.

(4) This case was a very complex one with a long history of chronic urinary infections and renal damage. This case was described by Houghton and Pears (1958) when low-potassium paralysis had developed from excessive self-purgation. At that time, and for some time after we began to look after her, the patient's total plasma-calcium levels were normal. They then rose with the development of the biochemical features of "primary" hyperparathyroidism. We wondered here whether her parathyroid adenoma could have developed as a result of long-standing secondary hyperparathyroidism from her renal damage.

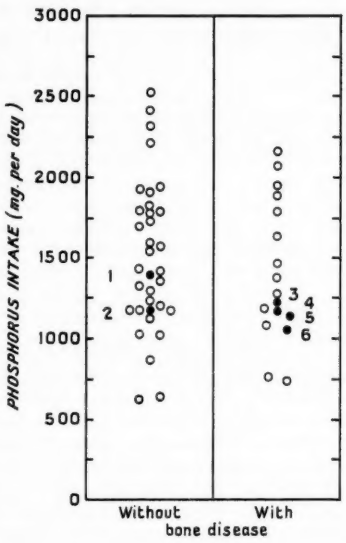

Fig. 2—Preoperative phosphorus intakes of patients with primary hyperparathyroidism.

The numbers and black circles refer to the patients similarly marked in fig. 1.

(5) This patient with classical signs of primary hyperparathyroidism is the only one in the series in whom we have been unable to find a tumour.

(6) This patient also had thyrotoxicosis.

Discussion

It seems clear from fig. 1 that our patients with primary hyperparathyroidism have all taken over 600 mg. a day of calcium in their diet, many taking much more than this. We unfortunately have no true control figures of our own of calcium intakes of subjects without hyperparathyroidism, but who are otherwise similar to the patients in question. Dietary population surveys, however, are readily available; and all indicate that daily calcium intakes of the order of 700 mg. or more are more than adequate for normal nutrition and are indeed taken by the populations of the wealthier Western European nations. For instance, the British Medical Association Committee on Nutrition (1950) noted that the average daily intake of calcium in urban working-class households was 605 mg. in 1941 and rose slowly to 996 mg. in 1947. They recommended a range of calcium intake of 0·8–2·0 g. per day as adequate for nutrition of people of both sexes under various normal conditions, including pregnancy. Many races seem to manage well on much lower intakes than this. We think that our figures argue strongly against any suggestion that preceding low calcium intake was the cause of formation of a parathyroid tumour. There is still a difficulty here in that many of our patients had probably had their disease for many years before coming to us. We should, therefore, have determined the dietary intake over the time when the tumour was developing, rather than after it had developed, as we must have done in at least some patients. This serious objection is not fully valid as our figures are all so unambiguously normal. We went back as far as we thought reasonable (five years) with the patients' memory of their previous diet. We think that the diet was unlikely to change greatly over the years since most adults' habits tend to be fairly invariable, and furthermore study of the individual clinical histories suggested no correlation between calcium intake and likely duration of the disease. In some patients the tumour is likely to have developed recently, and in these the dietary history would be truly relevant.

The second result obvious from fig. 1 is that there is no distinction between the calcium intakes in the group "with" and the group "without" bone disease. Both groups have taken over 600 mg. a day with a similar wide range, several of each group being on very high intakes. The average intake for the whole group of 17 with bone disease is 1408 mg. and for the 34 without bone disease is 1472 mg. We have not thought it worth while to dignify the results by working out further statistical embellishments. If anything, the patients with bone disease are more ill than those without, and it is surprising that a more obviously lower calcium intake should not have been found in this group. The timing of the diet survey cannot have affected this particular point since in all our cases with bone disease the disease was actively progressive and the duration of symptoms and signs was much shorter—often only a year or two—than in the group without bone disease.

Albright and Reifenstein (1948) suggested that a high calcium intake could protect a patient with primary hyperparathyroidism from osteitis fibrosa.

This hypothesis seemed to be based mainly on their very thorough study of one case—the first of this disease to be diagnosed in the U.S.A.—in which the difficult surgical problem (the tumour was only found after seven explorations) gave exceptional opportunities for long medical observation. They showed that he went into positive calcium balance only when the calcium intake was raised. In another patient put on a high oral calcium intake they found that over the next two years the skull X-rays showed great lessening of parathyroid changes. Dr. P. Henneman has very kindly sent us the original X-rays (the published reproductions were rather poor) and these convinced us of the correctness of the original X-ray reports. The full medical records, however, are not still available.

We inquired whether either of these two patients had also been taking any form of vitamin D during this period since we wondered whether this could have been more responsible for the lessening of the osteitis fibrosa than was the increased calcium intake. Certainly in secondary hyperparathyroidism, whether due to steatorrhœa or to chronic renal failure, vitamin D can at times completely dispel the radiological signs (Davies, Dent, and Willcox 1956, Dent, Harper, and Philpot 1961). Dr. Henneman was able to discover that the 2nd patient had taken some irradiated ergosterol during this period but could not determine the dosage details. This being in doubt we cannot now interpret the original findings, which seem at variance with what we would expect from our study, especially as detailed metabolic data indicated that the 1st of these 2 patients could be put into positive calcium balance when the intake was increased to only "above 0·6 to 1·0 g. of calcium per day". This intake was exceeded by most of our patients with bone disease.

A further argument against the hypothesis that calcium intake determines whether bone disease does or does not develop can be derived from the fact that the cases "with"

and those "without" it can be nearly always clearly distinguished from each other on the basis of radiological changes and plasma-alkaline-phosphatase levels. It is hardly to be expected that this sharp separation could occur were it dependent on dietary intake. It would be much more likely that the disease manifestations would show all degrees of severity in one continuous series. This argument has been raised already by one of us on other grounds in a preliminary communication (Dent 1959) which it is hoped to elaborate later. The work reported in this paper comprises part of our argument that the forms of primary hyperparathyroidism "with" and "without" bone disease are in fact different diseases presumably with differing circulating hormones being produced by the parathyroid tumours in question.

The data on phosphorus intakes shown in fig. 2 can be easily dealt with. Again, as with calcium, the intakes are all adequate and within the normal range, and there is no distinct difference between the groups "with" (average 1246 mg.) and "without" (average 1078 mg.) bone disease. There seemed a faint possibility that phosphorus might have been relevant to the study since, in renal osteodystrophy at least, it has often been suggested that the commonly found high plasma-inorganic-phosphate level could be responsible for stimulating the parathyroid gland.

Summary

An attempt has been made to estimate the dietary calcium and phosphorus intakes of 51 patients with primary hyperparathyroidism before they underwent parathyroidectomy.

No evidence has been found to suggest that a previous low calcium intake was a possible cause of the formation of parathyroid tumours.

There was no appreciable difference in calcium intakes between those patients with osteitis fibrosa and those without. This favours the possibility that a metabolic rather than a dietary cause is responsible for these two forms of primary hyperparathyroidism.

Phosphorus intakes also appeared to be all within the expected normal range.

We wish to thank Miss C. F. Harris, chief dietitian, University College Hospital, for her help and encouragement.

REFERENCES

Albright, F., Reifenstein, E. C. (1948) The Parathyroid Glands and Metabolic Bone Disease. London.
British Medical Association (1950) Report of the Committee on Nutrition. London.
Davies, D. R. (1959) *Proc. R. Soc. Med.* **52**, 995.
— Dent, C. E., Willcox, A. (1956) *Brit. med. J.* ii, 1133.
Dent, C. E. (1959) *Proc. R. Soc. Med.* **52**, 995.
— Harper, C., Philpot, G. (1961) *Quart. J. Med.* **117**, 1.
Houghton, B. J., Pears, M. A. (1958) *Brit. med. J.* i, 1328.
McCance, R. A., Widdowson, E. M. (1946) The Chemical Composition of Foods. *Spec. Rep. Ser., med. Res. Coun., Lond.* no. 235.

". . . With every new development in science we stumble over petrified words embodying mummified conceptions and such words impede our progress. The term general physician is one of such words and should be discarded, as it has been adopted in the days in which our knowledge of the human constitution and of the integrative functions of the organism was non-existent and 'general physician' was referring to the physician who dealt with all organic systems, in opposition to the narrow specialist. The role of the internist is different. He grasps intuitively the whole of the patient—the 'gestalt'—and combines the various organic findings. He is trained in 'integral thought', which, distinct from 'analytical thought', brings things together in a new pattern, integrates them, rather than breaking them into parts, relates the pieces to an integral whole. . . ."—Prof. A. P. CAWADIAS. *Brit. J. clin. Pract.* June, 1961, p. 509.

INFLUENCE OF THE WEATHER ON RESPIRATORY AND HEART DISEASE

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THE object of this study was to investigate the effects of certain meteorological variables on the incidence of respiratory disease, using a statistical technique which eliminates the large-scale seasonal fluctuations.

There are two main reasons for this approach. In the first place there will always be a fairly close correlation between any two seasonally varying quantities even though there is no direct connection between them. Secondly, the large seasonal variation in the meteorological variables introduces very high correlations between them which can completely swamp their minor, short-term fluctuations. These latter fluctuations can throw much light on the independent effects of the individual variables. For example, the average temperature in August is always higher than in January, and the relative humidity always lower, and to this extent temperature and relative humidity can hardly be considered to vary independently. But there can be warm, wet Augusts, or warm, dry ones and it is by comparison of warm and wet with warm and dry that the effects of humidity apart from temperature can be judged.

The method of analysis we have used, though not perfect, seems to us to be more trustworthy than one in which the seasonal trends are not eliminated, and it is also more effective in separating the effects of the different meteorological variables. On the other hand, it may be less sensitive, and the fact that it shows no significant correlation between two variables does not necessarily imply that no correlation exists.

Material and Methods

Data for the occurrence of disease were derived from the Emergency Bed Service (E.B.S.) of the King Edward Hospital Fund for London, and from records of admission to sick quarters in the Royal Air Force.

London

The applications for admission of acutely ill patients through the E.B.S. have in the past been regarded as a good index of the incidence of respiratory disease in London (Bradley et al. 1958, Abercrombie 1953, 1956). This assumption has been based on the sharp increase in demand on the E.B.S. which regularly occurs at an early stage of an outbreak of respiratory disease, and particularly on the sensitive way in which this rise mimics the rise in deaths during a pollution fog episode (Martin and Bradley 1960). Accordingly we decided to use the E.B.S. applications as our index of respiratory illness, and at the same time to test for correlations with cardiovascular disease, cerebrovascular accidents, and peptic ulceration. E.B.S. applications are classified by age into 18 general groups on the basis of the general practitioner's preliminary diagnosis. The four diagnoses chosen were each one of these groups.

In order to see what the relationship was between the E.B.S. admissions and patients admitted to hospital in the London

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region, we made use of data provided by the General Register Office on the Hospital In-Patient Enquiry (H.I.P.E.) for Greater London for one year, 1958. These figures provide a diagnosis for a 1 in 10 sample of all patients discharged from hospital in Greater London. We found a close relationship in the rate of admissions (E.B.S.) and discharges (H.I.P.E.) for respiratory disease at all ages and in both sexes. The relationship was less close for cardiovascular disease, while there was little relation in the peptic ulcer and the cerebrovascular-disease groups. We concluded from these comparisons that it was not permissible to use E.B.S. applications for testing correlations of weather variables with cerebrovascular diseases or peptic ulcer. We only use the E.B.S. figures for respiratory and heart disease for 1955–58.

The meteorological quantities examined were those recorded at Kew for mean daily barometric pressure (millibars), mean daily temperature (°F), mean absolute humidity (millibars), total rainfall (in.), total sun hours, and atmospheric pollution (as recorded by smoke concentration, mg. per c.m.) which are given in the Registrar General's weekly summary. The calendar month was used as the unit of time in all calculations as it was not only the most convenient in abstracting records but was also sufficiently long to smooth out some of the irregularities of weekly reporting, which are particularly noticeable in Royal Air Force and in the E.B.S. records when public holidays are present in a week.

Royal Air Force

Figures for the number of recruits and permanent staff admitted to sick quarters, hospital, or ill at home by reason of acute respiratory disease for forty-eight hours or more were available from three large recruit-training stations for varying periods (table I). The number of personnel in each category at

TABLE I—R.A.F. STATIONS PROVIDING DATA

Station	Corresponding meteorological recording station		Sex	Period for which data were available
Bridgnorth, Shropshire ..	Temperature, Relative humidity	Shawbury	M	1951–58
Hednesford, Staffordshire..	Temperature	Keele	M	1954–56
	Relative humidity	Elmdon		
Wilmslow, Cheshire ..	Temperature, Relative humidity	Speke	M and F	1952–58
	Atmospheric pollution	Hale 1		1955–58

these stations was available from monthly returns. These figures were obtained directly from the weekly notifications of all illnesses by stations to group headquarters (Stats 51). The accuracy of these figures has been checked previously (Holland, McDonald, and Wilson 1959) and found to give a true picture of the number of cases of acute respiratory disease at these stations. The mean daily temperature (°F), mean daily barometric pressure (millibars), total rainfall, and relative humidity at places near these stations were obtained from the Monthly Bulletin published by the Meteorological Department. Measurements of absolute humidity were not available, and those of atmospheric pollution were only available over limited periods for an area near one of these stations.

Statistical Methods

Details of the method of analysis used are given by Snedecor (1956) § 14·5. Its essence is to fit a mathematical formula expressing the incidence of the disease under consideration in terms of the meteorological variables. The constants in this formula, which are estimated from the data, are called multiple-regression coefficients, and they summarise the effect of a unit change in the corresponding variable on the incidence of the disease, independently of the changes in the other variables. It is this property that makes the technique valuable in the present connection. The values of these constants have been used to decide whether a given meteorological variable is

TABLE II—PARTIAL REGRESSION COEFFICIENTS AT VARIOUS AGES AND THEIR STANDARD ERRORS OF APPLICATIONS FOR ADMISSION THROUGH THE E.B.S., LONDON, OF PATIENTS DIAGNOSED AS SUFFERING FROM RESPIRATORY DISEASE, ON CERTAIN METEOROLOGICAL VARIABLES

Age (yr.)	Partial regression coefficients ($b \pm$S.E.)					
	Atmospheric pollution (smoke concentration mg./c.m.)	Mean daily temperature (°F)	Mean absolute humidity (millibars)	Total rainfall (in.)	Mean daily barometric pressure (millibars)	Total sun hours
0–4	−0·22 ±0·31	+0·068 ±0·085	−0·14 ±0·22	+0·14 ±0·14	−0·38 ±0·42	+0·65 ±0·49
5–14	+0·087 ±0·20	−0·035 ±0·055	+0·052 ±0·15	+0·019 ±0·09	+0·081 ±0·27	−0·16 ±0·32
15–64	+0·60* ±0·27	−0·15* ±0·07	+0·20 ±0·19	−0·13 ±0·12	−0·072 ±0·36	+0·23 ±0·42
65+	+0·66* ±0·23	−0·15* ±0·06	+0·20 ±0·17	−0·13 ±0·11	−0·25 ±0·32	+0·26 ±0·37

* Significant at 5% level.

effective in causing a change in the incidence of disease. If the corresponding regression coefficient does not differ significantly from zero as tested by its standard error, then the data, so far as they go, do not provide evidence that there is any relation between the two. The size of the regression coefficients is unrelated to the strength of association, and in this they differ from partial correlation coefficients.

The main disadvantages of the method are that it depends on relatively simple assumptions as to the mathematical relations between weather factors and disease, and that it takes no account of the fact that both disease and weather conditions tend to occur in " runs " so that values in neighbouring months tend to be correlated with one another.

The effect of the first drawback is usually to reduce the sensitivity of the method so that real effects may be missed. This implies that any effects found are correspondingly more firmly established.

The second disadvantage exaggerates the apparent significance of the results and may cause them to be taken as formally significant when they are not. The correlations between adjacent months in the present study are such as to reduce the effective degrees of freedom by about 50%. There are 8 degrees of freedom available in the E.B.S. data after fitting all constants and allowing for the correlations; this implies that the 0·05 level of significance for t was about 2·8. For the R.A.F. data 64 degrees of freedom were available, and allowing for the intercorrelations the significance level of t was therefore about 2·0.

Results

London: E.B.S. Applications

Non-respiratory disease.—No significant correlations between requests for admission through the E.B.S. and the meteorological variables described were found in any age-group for heart-disease.

Respiratory disease.—The partial regression coefficients and their standard errors for respiratory disease and the various meteorological variables are shown in table II. It may be seen from these that regressions on the edge of

TABLE III—PARTIAL REGRESSION COEFFICIENTS AND THEIR STANDARD ERRORS OF ADMISSIONS TO STATION SICK QUARTERS, HOSPITAL, OR SICK AT HOME OF MALE AND FEMALE RECRUITS AT 4 RECRUIT-TRAINING STATIONS, ON MEAN DAILY TEMPERATURE (°F) AND RELATIVE HUMIDITY

Sex and station	Partial regression coefficients ($b \pm$S.E.)	
	Mean daily temperature (°F)	Relative humidity
Male:		
Hednesford	−1·77 ±1·53	+0·05 ±1·28
Bridgnorth	−4·69 ±2·09*	+0·03 ±1·86
Wilmslow	−8·06 ±4·03*	−4·06 ±3·63
Female:		
Wilmslow	−7·76 ±3·15*	+4·82 ±2·84

* Significant at 5% level.

TABLE IV—PARTIAL REGRESSION COEFFICIENTS AND THEIR STANDARD ERRORS OF ADMISSION TO STATION SICK QUARTERS, HOSPITAL, OR SICK AT HOME OF MALE AND FEMALE PERMANENT STAFF AT 4 RECRUIT-TRAINING STATIONS, ON MEAN DAILY TEMPERATURE (°F) AND RELATIVE HUMIDITY

Sex and station	Partial regression coefficients ($b \pm$ S.E.)	
	Mean daily temperature (°F)	Relative humidity
Male:		
Hednesford	$-0{\cdot}62 \pm 0{\cdot}37$	$+0{\cdot}19 \pm 0{\cdot}31$
Bridgnorth	$-0{\cdot}90 \pm 0{\cdot}47$	$+0{\cdot}40 \pm 0{\cdot}45$
Wilmslow	$-0{\cdot}03 \pm 0{\cdot}47$	$+1{\cdot}06 \pm 0{\cdot}43$*
Female:		
Wilmslow	$-0{\cdot}95 \pm 1{\cdot}12$	$+1{\cdot}92 \pm 1{\cdot}01$

* Significant at 5% level.

statistical significance were found between applications for admission in those aged 15–64 and 65 or more years and atmospheric pollution and inversely for mean daily temperature, when the degrees of freedom available are adjusted for the intercorrelation between months.

Royal Air Force

The results obtained from Royal Air Force data are summarised in tables III and IV. Data on atmospheric pollution were available for only one of the stations. Since in this station there was little atmospheric pollution it is not surprising that no significant correlation between this factor and acute-respiratory-disease admissions was found. Among the recruits there was a significant negative correlation with temperature in Bridgnorth (for males) and in Wilmslow (for males and females), but relative humidity was not significantly related to respiratory-disease admissions. In the permanent staff at these stations no single significant correlation was found between the occurrence of acute respiratory disease and temperature. At Wilmslow a positive correlation with relative humidity in male permanent staff is shown. The pooled estimate of the regression of acute respiratory disease on temperature for male and female recruits is $-3{\cdot}80 \pm 1{\cdot}10$, which is formally significant, as is the pooled regression coefficient for the permanent staff—$-0{\cdot}539 \pm 0{\cdot}246$. The regression coefficients on relative humidity are also significant when pooled in this way, their values being $+0{\cdot}298 \pm 0{\cdot}095$ for the recruits and $+0{\cdot}523 \pm 0{\cdot}214$ for permanent staff.

Discussion

The evidence presented above indicates that both atmospheric pollution and low temperature have an effect on the admissions to London hospitals of patients aged more than 15 years with acute respiratory disease. It is impossible to decide from our data whether pollution or low temperature has a greater effect, but it does seem that each can exert an effect independent of the other. The effect of low temperature on the incidence of respiratory disease is confirmed by examination of the sickness notifications in certain Royal Air Force recruit stations. No positive correlations were found between applications for admission for heart-disease through the E.B.S. and the various meteorological variables examined.

The statistical significance of these findings is difficult to judge. In view of the large number of regression coefficients examined it is to be expected that one or two might be significant at the 5% point by chance alone. However, the close correspondence between the regression coefficients of E.B.S. applications for respiratory disease on atmospheric pollution and mean daily temperature in two different age-groups, and the independent confirmation of the temperature effect provided by the Royal Air Force data, leave little doubt that a genuine relationship exists.

The pooled estimates of the regression of respiratory disease on temperature in R.A.F. recruits and permanent staff were formally significant. This was also the case for relative humidity, but the E.B.S. figures show no significant association between humidity and respiratory disease, and, taking this into account, the relationship in the Royal Air Force data, which is rather irregular, is still open to question.

These findings confirm the ill-effects of low temperature and atmospheric pollution on mortality noted by others.

Farr (1885) drew particular attention to the effect of seasons and weather on mortality. He noted that the commonest causes of death in the cold months belonged to the pulmonary class and the cerebral diseases of the aged, but he did point out that many cases classified under apoplexy were probably due to "congestion of the lungs". The effect of atmospheric pollution on mortality has been recorded on numerous occasions both by Farr and by more recent workers such as Logan (1953) and Gore and Shaddick (1958). Reid (1958) reviewed the evidence of the effect of environmental factors in respiratory disease and noted particularly the effect of air pollution on respiratory disease, especially in older men. Boyd (1960), analysing mortality data in London and East Anglia, found respiratory mortality to be most closely associated with temperature and humidity in the two weeks immediately preceding death, but he was unable to separate the effects of humidity and temperature. The association was particularly noticeable in those aged 45 years or more and less distinct in the younger age-groups. He also found associations with pollution, particularly sulphur-dioxide content. The more serious effects of urban fog appeared only to occur when fog was accompanied by very low temperatures, but his study differs from ours in that seasonal variations were not eliminated and he was dealing with mortality.

No effect of atmospheric pollution on respiratory disease in children is evident in our data. Russell (1924, 1926) found an association between death from respiratory disease and fog in persons aged more than 55 years, but none in children.

From our figures it is clear that a low temperature is associated with an increase in respiratory disease in adults apart from any effects of atmospheric pollution. When low temperature and atmospheric pollution act together their effect is particularly clear, as in the 1952 "fog incident" when there was temperature inversion.

Young (1924) showed that in children there was an association between deaths from bronchitis and pneumonia and the mean temperature of the preceding week. Woods (1927) showed that in children there was an association between deaths from pneumonia and low temperature in those aged less than 40 years, but not in children aged less than 5 years. Payling Wright and Payling Wright (1945), however, analysing the data for 1923–39, indicated that mortality from bronchopneumonia in both infants (aged 0–2 years) and the elderly (aged more than 55 years) rose rapidly when the mean daily temperature fell below 40°F. Hope Simpson (1958) has also suggested that there is an association between the incidence of common colds and fall in temperature.

We have been unable to confirm these findings in children, but our study differs in that we used the age-group 0–4 years and eliminated both the seasonal effect and short-term fluctuations. The apparent absence of an association between respiratory-disease admissions in children and temperature may indicate that admission to hospital is not a reliable index of the incidence of respira-

tory disease in children in the community. Other factors, such as the social environment, probably play a very much bigger part in their admission than illness alone. Furthermore, low correlations will be masked by errors in the variables and by departure from linearity of regression, and short-term associations will tend to be missed by the monthly grouping of the figures.

The associations we have found give no indication of the mechanisms by which cold and atmospheric pollution produce their effects. Nungester and Klepser (1938) showed that rats sprayed with cold water were more liable to develop pneumonia, and they produced some evidence that this was due to enhanced aspiration of mucus and diminution of the glottal reflex in the cold. More recently Wells et al. (1960) have shown that certain patients with chronic respiratory disease which becomes worse in cold weather show an increase in airflow resistance when exposed to very cold air (−40°C to −20°C), which is relieved by bronchodilator substances. The action of cold could, however, be more simply explained by the tendency of people to stay indoors and decrease ventilation with a correspondingly greater chance of spreading infection. The effect of atmospheric pollution on the old rather than the young may be explained by the greater integrity of the respiratory-tract mucous membranes in the young.

Summary

The figures for application for admission through the Emergency Bed Service (E.B.S.) in London in 1955-58 for respiratory disease and heart-disease were examined for their correlations with various meteorological factors after eliminating the seasonal trends. A correlation between respiratory disease and temperature and atmospheric pollution was found for those aged 15–64 and more than 65 years.

The effect of temperature on the incidence of acute respiratory disease was confirmed in a study of its incidence at three Royal Air Force recruit-training stations. No significant correlation was found with atmospheric pollution, but this may have been because data were available for only one station, which was in a semirural area.

We wish to thank Commander J. R. E. Langworthy, of the Emergency Bed Service, Dr. M. A. Heasman, of the General Register Office, Group Captain R. J. A. Morris and Mr. W. A. B. Milligan, of the Air Ministry, and Mr. A. J. Sharp, of Warren Spring Laboratory, for helping us in the collection of data; the statistics department at Rothamsted Experimental Station for help in analysing much of the data on the electronic computer there; and the Director General, Medical Services of the Royal Air Force, for permission to publish the findings in the Royal Air Force.

REFERENCES

Abercrombie, G. F. (1953) *Lancet*, i, 234.
— (1956) *ibid.* ii, 1039.
Boyd, J. T. (1960) *Brit. J. prev. soc. Med.* **14**, 123.
Bradley, W. H., Logan, W. P. D., Martin, A. E. (1958) *Mon. Bull. Min. Hlth Lab. Serv.* **17**, 156.
Farr, W. (1885) Vital Statistics. London.
Gore, A. T., Shaddick, C. W. (1958) *Brit. J. prev. soc. Med.* **12**, 104.
Holland, W. W., McDonald, J. C., Wilson, J. S. (1959) *Mon. Bull. Min. Hlth Lab. Serv.* **18**, 65.
Hope Simpson, R. E. (1958) See *Brit. med. J.* i, 214.
Logan, W. P. D. (1953) *Lancet*, i, 336.
Martin, A. E., Bradley, W. H. (1960) *Mon. Bull. Min. Hlth Lab. Serv.* **19**, 56.
Nungester, W. J., Klepser, R. G. (1938) *J. infect. Dis.*, **63**, 94.
Payling Wright, G., Payling Wright, H. (1945) *J. Hyg., Camb.* **44**, 15.
Reid, D. D. (1958) *Lancet*, i, 1237, 1289.
Russell, W. J. (1924) *ibid.* ii, 335.
— (1926) *ibid.* ii, 1128.
Snedecor, G. W. (1956) Statistical Method. Ames, Iowa.
Wells, R. E., Walker, J. E. C. Hickler, R. B. (1960) *New Engl. J. Med.* **263**, 268.
Woods, H. M. (1927) *J. Hyg., Camb.* **26**, 36.
Young, M. (1924) *ibid.* **23**, 151.

XANTHOMATOUS BILIARY CIRRHOSIS TREATED WITH CHOLESTYRAMINE

A Bile-acid-adsorbing Resin

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A PATIENT with xanthomatous biliary cirrhosis whose plasma-lipids returned nearly to normal during the intake of a diet containing large amounts of linoleic acid was described by Walker, Flynn, and Kinsell in 1959. Because of subsequent interesting developments, the following further report on this patient is submitted.

Case-report

In 1956 a white woman, now aged 45, had an insidious onset of fatigue, pruritis, occasional abdominal discomfort, and slowly progressing jaundice, shown to be of an obstructive type. Extrahepatic biliary exploration had shown no abnormality, but cholecystectomy was performed. Her symptoms persisted and in March, 1957, she noted small, tender, yellow nodules which began on her hands and soon involved the skin of all parts of her body. Prior to 1956 she had had no significant serious illness; she had no history of hepatitis or of exposure to toxic chemicals.

In February, 1958, the patient was admitted to the metabolic ward and was treated with a 2200-calorie formula diet which contained 80 g. of ethyl linoleate. All her plasma-lipids tended to return toward normal values, her icterus decreased, and her xanthomata completed disappeared; she returned home, where she was able to do her housework and care for her family. During the three months before her original admission she had been confined to bed because of weakness and general malaise.

In February, 1960, the patient stated that she had "flu". Her lipids and bilirubin increased moderately. Corticoid therapy was instituted on the assumption that she had low-grade cholangitis. Lipids and bilirubin decreased briefly to some degree, but the patient did not feel at all well. Corticoids were discontinued, and bilirubin and lipids rose over the period from April to August, 1960, despite increase in dietary poly-unsaturated fat. Therefore, on Aug. 1, 1960, the patient was readmitted to the metabolic ward.

Examination

On admission her weight was 129 lb., which was proportional to her height and body-build. Her general nutrition was fair. The skin was dry and olive-coloured, but there were no definite xanthomata. The sclera were quite yellow. The liver edge was palpable 2 cm. below the right costal margin in the mid-clavicular line.

Admission Laboratory Findings

Total lipids were 3163 mg. per 100 ml.; free cholesterol 1130 mg. per 100 ml.; cholesterol esters 90 mg. per 100 ml.; phospholipids (as lecithin) 2070 mg. per 100 ml.; free fatty acids 1·67 mEq. per litre. Alkaline phosphatase was 16 Bodanski units per 100 ml., and total bilirubin was 11·4 mg. per 100 ml. Urinalysis was normal. Hæmoglobin was 11·8 g. per 100 ml.; leucocytes 6400 per c. mm. with a normal differential count.

Treatment

On admission the patient received a 2000-calorie formula diet which contained 100 g. protein, 80 g. ethyl linoleate, and 20 g. safflower oil. After seventeen days an additional 20 g. of ethyl linoleate was added. In an effort to provide even more unsaturated fat, an intravenous emulsion of cottonseed oil ('Lipomul') was administered on Sept. 1, 1960. However,

during the administration of the emulsion the patient developed a pruritic dermatitis, which was treated with anti-histamines; and no further intravenous fat emulsion was given.

On Sept. 12, 1960, administration of a resin with a specific affinity for bile acids (see below) was begun. The bile-acid-binding capacity of this resin in man was first described by Hashim et al. (1961). The dosage was 14 g. per day, in divided dosage. The chemical response is shown in fig. 1. There was a rapid fall in plasma-bile acids, followed by a precipitous decrease in all plasma-lipids except cholesterol esters. These latter had been abnormally low. They rose to a level at which the free/ester cholesterol ratio was within the normal range. Over the next several months there was also a progressive fall in plasma-bilirubin.

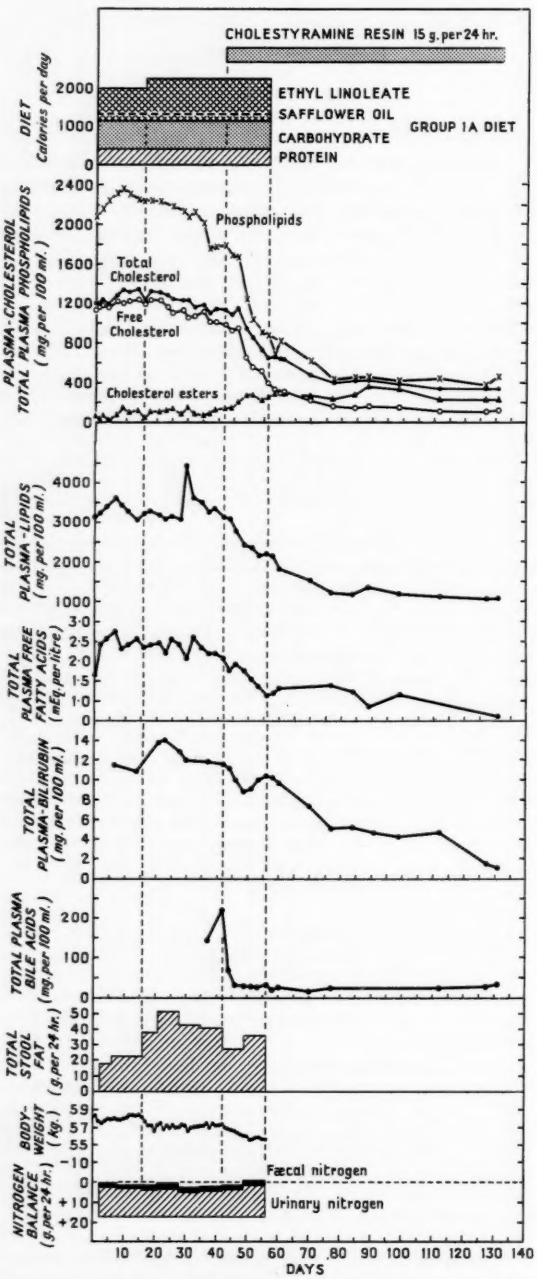

Fig. 1—Biochemical response.

Plasma-lipids, which had decreased only slightly with intake of large amounts of ethyl linoleate, fell precipitously when cholestyramine was administered. Plasma-bile-acids fell immediately, and plasma-bilirubin gradually decreased.

Three studies with ^{14}C mevalonic acid (a cholesterol precursor) were carried out in this patient, the first during her initial remission, the second during her exacerbation, and the third during her second remission in association with resin administration. 4 μC of ^{14}C D.L. mevalonic acid was administered intravenously, and blood was taken at the intervals noted in fig. 2. ^{14}C content of free and esterified cholesterol was determined in a 'Tricarb' scintillation counter after extraction and isolation of the sterols from the plasma and appropriate preparation with phosphors. Values are reported as per cent of administered dose per approximate plasma-volume. In the interpretation of these data the following variables must be considered:

1. The size of the mevalonic-acid pool—regarded for present purposes as a constant.
2. The rate of excretion of mevalonic acid—regarded as constant.
3. The rate of metabolism of ^{14}C mevalonic acid to ^{14}C plasma-cholesterol.
4. The rate of removal of ^{14}C cholesterol from the plasma during the period included in the study, either for use by cells, oxidation to bile acids, or excretion in the bile as cholesterol.

The data obtained cannot be interpreted in an absolute sense, but should have comparative value.

In A and B of fig. 2, the values for ^{14}C cholesterol concentration are the highest found in any individual thus far studied. In A not only is the level high, but the rate of removal is rapid (8–24 hours). In B the level is high, and the rate of removal slow. From this it seems most probable that the rate of cholesterol synthesis in A is much greater than in B, since maximal plasma concentrations are equal in each case.

In C maximal concentration is only moderately greater than normal, and rate of removal is decreased.

Unfortunately, data regarding bile-acid concentration are not available at the time of the A and B mevalonic-acid studies. It is known, however, that plasma-bile-acids fell to a significant degree during the first remission with ethyl-linoleate feeding. During this remission the patient complained at all times of much pruritis. In the C period (see fig. 1) the bile acids fell profoundly and pruritis disappeared.

It seems probable that the fall in lipids during period A was attributable to major acceleration of cholesterol excretion, despite a very high rate of cholesterolgenesis. During the B period the chief factor responsible for the high cholesterol level was impaired cholesterol excretion, probably largely attributable to decreased bile-acid excretion. The elevated level of cholesterol may have inhibited cholesterol formation somewhat. During the C period it was obvious that the total excretion of bile acid was greatly increased. In association with this, there appeared to be a major decrease in rate of cholesterolgenesis.

Discussion

Three questions require consideration:

1. *Was the exacerbation of the biliary cirrhosis in any way related to corticoid administration?*

The preparation used was prednisone administered in a maximal dosage of 15 mg. daily over a total period of ten weeks. As noted, it was administered in the hope that it would inhibit cholangiolitis and result in complete disappearance of the residual jaundice. This did not occur. Actually, the exacerbation very probably began before corticoid therapy was started. If the association was not coincidental, the explanation would lie somewhere in the interrelationship between cholesterol metabolism, bile-acid metabolism, and cortical steroid metabolism.

2. *Why did this patient not respond satisfactorily to poly-unsaturated fatty acid therapy, as she did initially?*

No adequate answer is available, but the data in the

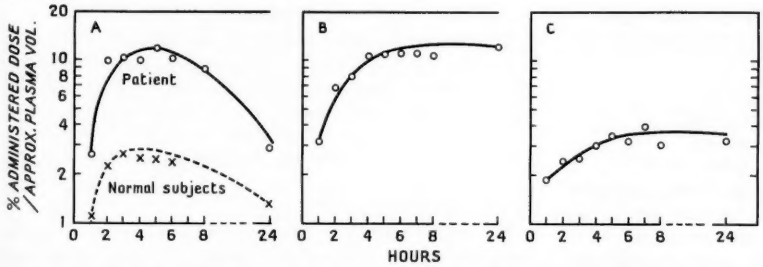

Fig. 2—Comparative rates of conversion of ^{14}C mevalonic acid to cholesterol in the three phases of the study.

Initial decrease in lipids in response to ethyl linoleate would appear to be attributable chiefly to increase in rate of removal, despite a high rate of synthesis. During the second remission, the rate of conversion appears to be much diminished.

A. During initial remission (on ethyl linoleate) fasting plasma values (mg. per 100 ml.) were as follows: total cholesterol 316 (free 161, ester 155); total lipids 1156; phospholipids 540.

B. During exacerbation (on ethyl linoleate) fasting plasma values (mg. per 100 ml.) were as follows: total cholesterol 1190 (free 1130, ester 60); total lipids 3163; phospholipids 2070.

C. During second remission (on cholestyramine resin): fasting plasma values (mg. per 100 ml.) were as follows: total cholesterol 630 (free 332, ester 298); total lipids 2156; phospholipids 700.

accompanying table may have some bearing. During the high linoleic-acid intake associated with the initial remission, the patient had a very high linoleic-acid content of the cholesterol esters. During the intake of an equal amount of linoleate in period B, the cholesterol linoleate was abnormally low. In the early portion of period C, this was increasing. Also, during period B there was a high content of short-chain acids and unidentified long-chain and/or polyunsaturated acids in the cholesterol esters during the exacerbation. Apparently, in period B a block prevented esterification of the linoleic acid with cholesterol (Sperry and Stoyanoff 1937). The mechanism of this block and its relation to the total biochemical-clinical picture is still obscure. It is of interest that on Nov. 21, 1960, when the patient had been on the resin for over two months, the cholesteryl linoleate was 70% of the total cholesterol esters.

3. *The third question concerns the mechanism of the striking response to cholestyramine,* a quaternary ammonium anionic exchange resin with specific affinity for bile acid.*

1 g. of this resin was found by Tennent et al. (1960) to adsorb 91·4% of a 1% solution of sodium cholate in a volume of 100 ml. Siperstein et al. (1953) showed that the plasma-cholesterol rise in cholesterol-fed cockerels can be inhibited by feeding ferric chloride and associated this effect with the precipitation of bile acid in the intestinal tract. They suggested that binding of bile acids may serve as a means of controlling serum-cholesterol. In the present case, since there is apparently serious interference with bile excretion, as is indicated by the jaundice, it seems not improbable that the binding and subsequent excretion of bile acid by the resin results in increased excretion of bile acid through the intestinal wall. The efficacy of this process is indicated by the fall in total plasma-bile-acids from 168 μg. to 24 μg. per ml. of plasma within a week after the institution of the resin therapy.

In animal studies with this resin no significant side-effects were noted except steatorrhœa with extremely high doses; no vitamin-K deficiency or deficiency of other fat-soluble vitamins was observed. In our patient, after four months on the resin a pronounced bleeding tendency was observed, and her plasma-prothrombin level was found to be 19% of normal. This difficulty was promptly resolved by administration of parenteral vitamin K.

The fall in bilirubin with continued administration of the resin indicates progressive increase of bile output.

*This material, known as MK-135, was synthesised in the Merck Institute and was supplied to us through the kindness of Dr. Edwin DeMaar.

PERCENTAGE FATTY-ACID COMPOSITION OF PLASMA-LIPID COMPONENTS† (By Gas-Liquid Chromatography)

Period	Fatty-acid chain: All less than C_{14}	C_{14}	C_{16}	$C_{16:1}$	C_{17}	C_{18}	$C_{18:1}$	$C_{18:2}$	$C_{18:3}$	All over $C_{18:3}$
Cholesterol-ester Fraction:										
A	..	1	10	4	..	tr	6	77	..	..
B	14	8	13	8	10	7	5	27	..	6
C	3	6	15	4	2	1	15	46	1	5
Glyceride Fraction:										
A	..	2	24	4	..	17	25	29	..	..
B	3	2	23	6	..	6	19	42	..	..
C	..	2	21	6	tr	3	20	48	tr	..
Phospholipid Fraction‡:										
B	8	4	32	..	8	16	10	23	..	..
C	tr	1	37	2	..	14	11	25	..	4
Free-fatty-acid Fraction‡:										
B	10	4	26	..	10	12	14	20	1	..
C	4	3	25	6	2	8	23	29	..	..

Period A: during first remission (on ethyl linoleate).
Period B: during exacerbation (on ethyl linoleate).
Period C: during second remission (on cholestyramine resin).
†Each figure is the average of the final three determinations performed during each clinical period.
‡This determination was not done during period A.

Summary

A patient with biliary cirrhosis, who has been previously reported as responding to a diet high in polyunsaturated fat, had a severe exacerbation which may or may not have been related to administration of prednisone. Increased dietary intake of polyunsaturated fat did not produce an adequate remission.

Administration of an exchange resin with specific affinity for bile acids resulted in a rapid fall in the level of plasma-bile-acids and of all the plasma-lipids except esterified cholesterol, which had been pathologically low and which now rose to normal levels.

Since liver function was not severely disturbed, it seems probable that the initially high free cholesterol and low esterified cholesterol were due to inhibition of esterification of cholesterol in the plasma by the high bile-acid titre. Long-continued administration of the resin was associated with vitamin-K deficiency, which promptly responded to parenteral administration of vitamin K.

REFERENCES

Hashim, S. A., Bergen, S. S., Van Itallie, T. B. (1961) *Proc. Soc. exp. Biol., N.Y.* **106**, 173.
Siperstein, M. D., Nichols, C. W., Jr., Chaikoff, I. L. (1953) *Science*, **117**, 386.
Sperry, W. M., Stoyanoff, V. A. (1937) *J. biol. Chem.* **121**, 101.
Tennent, D. M., Siegel, H., Zanetti, M. E., Kuron, G. W., Ott, W. H., Wolf, F. J. (1960) *J. Lipid Res.* **1**, 469.
Walker, G., Flynn, P. F., Kinsell, L. W. (1959) *Lancet*, i, 286.

Addendum

The increased prothrombin-time noted during prolonged administration of the resin was promptly counteracted by parenteral vitamin K. Subsequent administration of 5 mg. of vitamin K by mouth maintained a completely normal prothrombin-time. There has been no evidence of any other fat-soluble-vitamin deficiency.

DEPOT-METHYLPREDNISOLONE FOR SUBCONJUNCTIVAL AND RETROBULBAR INJECTIONS

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THIS study aimed to establish whether a new compound 6α-methylprednisolone was suitable for subconjunctival and retrobulbar injection. This drug was developed primarily as a long-acting steroid for intramuscular and intra-articular use. Each millilitre of the tested preparation * contains 40 mg. of 6α-methylprednisolone acetate and 30 mg. polyethylene glycol in a sodium-chloride vehicle with myristyl-γ-picolinium-chloride 1/5000 as preservative. I investigated: (1) tolerance of the ocular tissue to this preparation; (2) the possibility of giving fewer steroid injections (a much higher dose of corticosteroid is possible with methylprednisolone than with cortisone or hydrocortisone); and (3) substitution of subconjunctival and retrobulbar injection for oral steroid therapy, which is expensive and can have side-effects.

* 'Depo-Medrone', Upjohn.

Method

The patients were divided into two groups:

(1) New patients who would normally be treated with subconjunctival or systemic steroids, and those patients who did not respond to topical therapy.

(2) Patients already being given steroids by mouth. The dose was gradually reduced; and steroid injected near the lesion instead.

Subconjunctival Injection

The local anæsthetic was lignocaine ('Xylocaine'), 2% with adrenaline. 1 drop every minute for five minutes was usually sufficient. Depo-medrone (0·2 ml.) was injected 4 mm. from the limbus, either above or below the cornea (if the anterior chamber was affected); or directly over a lesion situated in the episclera or sclera. The injections were repeated either every two weeks, or when the signs of the previous one had disappeared, whichever was the longer.

Retrobulbar Injection

This method was chosen for conditions affecting the choroid and retina. I did not find local anæsthesia necessary. Depo-medrone (0·5 ml.) was injected and the dose repeated in three to four weeks, according to the patient's progress.

In both groups mydriatics and antibiotics were given as necessary.

TABLE I—NEW PATIENTS AND PATIENTS NOT RESPONDING TO TOPICAL THERAPY

Case no.	Clinical condition	Injections		Result	Follow-up (months)
		Subconjunctival	Retrobulbar		
1	Deep keratitis; treated with atropine and oxytetracycline, hydrocortisone acetate, and polymyxin B ('Terracortril') for 5 months	3 at four-weekly intervals		Settled after the second injection	4
2	Episcleritis for 1 month not responding to prednisolone phosphate ointment ('Predsol')	1		Cured	1
3	Peptic ulcer; scleritis for 7 months not controlled by predsol	4 at two-weekly intervals		Settled after two months' treatment	3
4	Macular œdema; visual acuity 3/60		3 at three-weekly intervals	Visual acuity 6/12–2 after six weeks of treatment	5
5	Acute iridocyclitis for 1 month, not controlled by atropine sulphate, cocaine hydrochloride, adrenaline acid tartrate, sodium chloride, and chlorbutol ('Mydricaine'), and terracortril	3 at two-weekly intervals		Settled (apart from mild aqueous flare) after third injection	3
6	Choroiditis		2 at four-weekly intervals	Cured	3
7	Iridocyclitis with hypopyon; diabetes; hypopyon cleared with subconjunctival penicillin	5 at four-weekly intervals		Settled (apart from mild aqueous flare) after second injection	4
8	Recurrent, acute, bilateral iridocyclitis not controlled by topical treatment	6 at four-weekly intervals to alternate eyes		No recurrence apart from occasional mild ciliary injection	8
9	Recurrent choroiditis; septic tooth removed under penicillin cover		2 at four-weekly intervals	Cured	4
10	Acute exacerbation of chronic iritis	3 at two-weekly intervals; 2 at four-weekly intervals		Settled after second injection	5

TABLE II—PATIENTS RECEIVING STEROIDS BY MOUTH

Case no.	Clinical condition	Injections		Result	Follow-up (months)
		Subconjunctival	Retrobulbar		
1	Chemical injury: deep keratitis, iritis, and hypopyon; hypopyon cleared by subconjunctival penicillin; otherwise not controlled by oral methylprednisolone ('Medrone'); rapidly gaining weight	3 at two-weekly intervals		Rapid improvement after the first injection; quiet after three injections	5
2	Recurrent iridocyclitis normally controlled by oral medrone	2 at two-weekly intervals		Acute attack subsided	5
3	Bilateral chronic iridocyclitis; steroids by mouth for three years; gaining weight; acne	3 into each eye at four-weekly intervals		No need for further steroid therapy; both eyes quiescent	6
4	Bilateral scleritis with right secondary iritis and glaucoma; right filtering scar operation; for two years fairly well controlled by oral medrone; gaining weight; acne and boils	1 into each eye		Scleritis flared up; brought under control with oral medrone	1
5	Recurrent bilateral iridocyclitis controlled by oral medrone; gaining weight	3 into each eye at three-weekly intervals		Both eyes quiet after 2 injections; another exacerbation two months later, controlled by single injection into each eye	8

Results

Over a period of six months, 15 patients—10 new ones, and 5 already being given steroids by mouth—were studied. The diagnosis, method, and frequency of treatment, and the results are summarised in tables I and II.

Discussion

Corticosteroids given by the subconjunctival or retrobulbar route can often produce an excellent clinical response; and since the quantity injected is small, systemic side-effects are virtually eliminated. With simple hydrocortisone preparations absorption is fairly rapid, and injections have to be repeated frequently; relatively small amounts only of steroid can be given because the volume is limited by the method of administration. These disadvantages are overcome by a steroid preparation which is highly concentrated, and has a depot effect, provided it is well tolerated by the ocular tissues. Depo-medrone fulfils these criteria. It has been reported to maintain corticosteroid control for over a week when given intramuscularly for dermatological conditions (Smith 1959, Alexander and Harvey 1960); given intra-articularly in rheumatoid arthritis, its mean period of action was 51 days (Woodbury and Biechl 1960).

I did not treat enough patients to allow statistical analysis; but the experiment lasted sufficiently long for confident conclusions to be drawn:

(1) The ocular tissues tolerate injections of depo-medrone very well.

(2) Subconjunctival injections will seldom be needed more often than once every two weeks. None of my patients required more frequent injections.

(3) Control for four weeks results from a single retrobulbar injection.

(4) After injections near the lesion are begun, it is unlikely that oral therapy will be needed. This was true for all my new patients and for patients not responding to topical therapy.

(5) Steroids by mouth were successfully discontinued in all patients but one. Subconjunctival or retrobulbar depo-medrone therefore appears to be a good substitute in most cases for steroids by mouth. Its effect in some instance, may even be greater (see case 1, table II).

Summary

The effect of 'Depo-Medrone' injected near eye lesions has been found superior to that of cortisone. The greater effect of a much higher single dose absorbed over a longer period makes steroids by mouth necessary for only a few patients. There were no complications, and local tolerance to the preparation was uniformly good.

REFERENCES

Alexander, J. O'D., Harvey, G. (1960) *Lancet*, ii, 437.
Smith, H. G. (1959) *Curr. Ther. Res.* **1**, 122.
Woodbury, J. F. L., Biechl, A. (1960) *Canad. med. Ass. J.* **83**, 836.

Preliminary Communications

A TECHNIQUE FOR STUDYING HUMAN TUMOUR GROWTH IN VIVO

BECAUSE much progress has been made in the treatment of certain forms of cancer by hormone-depriving operations, chemotherapy, and new radiation techniques, the need for an in-vivo method of assessing human tumour growth arose. Such a method would enable one to select cases for the most appropriate treatment, to assess the response, and to follow certain lines of research. A technique has been developed over the past four years which is proving useful in this respect.

THEORY

Phosphorus, which is incorporated into tumour cells during the process of growth, plays an important role in the synthesis of desoxyribosenucleic acid (D.N.A.), the maximum concentration being reached late in prophase before mitosis occurs. Phosphorus also enters into the mechanism of glycolysis, glycogen being changed to glucose and inorganic phosphate under the influence of the enzymes phosphorylase and phosphatase. There is an exchange of phosphorus between the cell and the extracellular fluid, and this turnover of phosphorus can be used to indicate the degree of neoplastic activity. Hence, the influence on a tumour of drugs, hormones, and radiation techniques can be studied if the concentration of phosphorus can be measured over long periods.

Radioactive phosphorus (^{32}P) was used as an indicator and the activity was recorded from within tumours. It seemed important to record from *within* to get the highest counting-rate from the beta radiation, and to avoid factors which cause inaccuracies in surface counters. These include alteration in counting-rate due to different pressures of application, and changes in blood-supply of the skin and other tissues. For part of this study it was necessary to have information from several places within a tumour at the same time. The Geiger-type needle-probe counters developed commercially were intended for short-term single recordings of uptake in brain tumours. These probes seemed the obvious choice for my purpose if they could be made to last long enough, but this proved very difficult because the small physical dimensions of the tube inevitably meant a short life. The problem was overcome by using a time-switching device which activated a series of probes in turn for periods of three minutes in every half-hour or hour. This and other modifications to the apparatus made it possible to extend counter life more than adequately, and information can now be recorded for days or weeks if necessary.

Fig. 1—The machine in use, mounted on a trolley. The printing counter is shown on top.

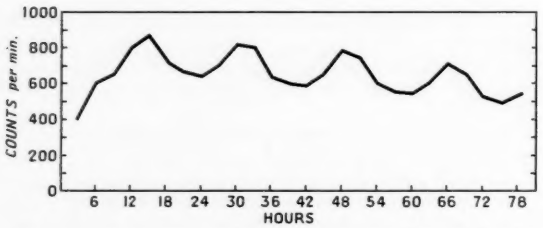

Fig. 2—A typical tracing, showing a regular cycle of growth activity in a hormone-sensitive breast cancer.

APPARATUS

One or more Geiger needle probes is connected by a short length of coaxial cable to a cathode-follower valve placed near the patient. For technical reasons this cable must be short—not longer than about 18 inches. This valve is linked to the time-switching mechanism, and in turn it feeds information from the probes to an ordinary ratemeter connected to a machine which prints the required figures on to a roll of paper. Check pulses from various parts of the apparatus are also recorded, and, provided these remain constant, any variations in the figures obtained from the probes must be significant.

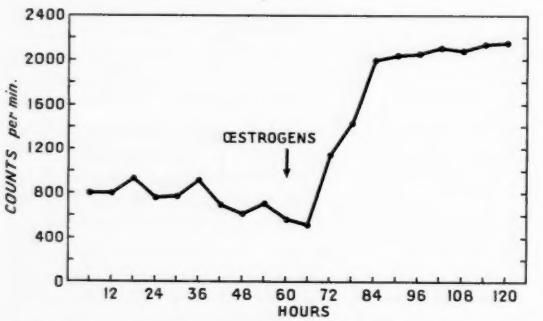

Fig. 3—The response of an œstrogen-dependent breast tumour to that hormone. The counting-rate has greatly increased within twenty-four hours.

METHOD

The probes are sterilised chemically and one is inserted, under local anæsthesia, into the growth, and another into a control point, if necessary. The insertion is made through a small stab wound, produced by a hydrocele trocar and cannula. The trocar is removed and the probe counter is inserted in its place. The cannula is then withdrawn just over a centimetre, to leave the actively recording portion of the probe exposed within the tumour. The cannula affords good support for the rather thin-walled probe, and prevents it being bent. The instrument is then held in position by adhesive tape over a foam-rubber support.

After about twenty minutes, when any bleeding has ceased, a tracer dose of 500–750 microcuries of ^{32}P is given by mouth. Recording then starts, and it continues entirely automatically for as long as necessary (fig. 1). The patients (who have all been adults) are kept in bed throughout the test, and none has reported any unpleasant discomfort; they have been most helpful, and have usually shown keen interest in the proceedings.

CLINICAL APPLICATIONS IN BREAST CANCER

This seemed the most logical to study first, as such cases are readily available, and the growths are easily accessible. The cases were divided into two groups with different objectives in view:

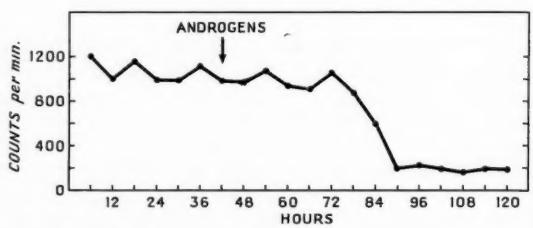

Fig. 4—The rate of growth of an œstrogen-dependent breast tumour treated with androgens.

1. *To determine whether there is any Regular Cycle of Growth Activity*

From the cyclical behaviour of certain endocrine systems one might expect hormone-dependent tumours to show a regular variation of mitotic activity under the influence of the pituitary or other glands. If so, the time of day when the tumour is most radio-sensitive could be selected for treatment.

Multiple probes were used for this investigation to make certain that the resulting information was representative of the tumour as a whole, and not merely of the area immediately around one probe.

Of 75 cases studied 25 showed a regular cycle of growth activity. Fig. 2 is from one of these. The peaks were at ten to seventeen hours, and the average interval between them was thirteen hours. The cycle was independent of time of day, exercise, eating, sleeping, or the particular histology of the breast growth. All the 25 cases showing this cycle proved to be hormone dependent.

44 cases showed cyclical variations but no regular rhythm, as far as could be determined in the period studied. 14 of these later proved to be hormone dependent.

6 cases showed no significant variation in activity and merely took up the phosphorus to a rather low and steady level. These were all atrophic scirrhous growths in elderly patients. Such tumours often remain quiescent for long periods.

2. *To see whether this Technique can be used to detect Hormone Dependence*

This knowledge would then provide a means of selecting cases for hormone-depriving operations, such as oophorectomy and hypophysectomy, or for hormone therapy.

A base-line of phosphorus uptake was obtained over a period of forty-eight hours, and then one could see how the counting-rate was influenced by administering hormones. It was found to be quicker to stimulate an œstrogen-dependent tumour with stilbœstrol than to suppress it with androgens. Stilbœstrol was given in gelatin capsules which seemed to minimise gastric reaction, and the dosage used was 15 mg. t.d.s. This method usually gave a result within twenty-four to thirty-six hours. In some cases a significant alteration in uptake was observed within twelve hours of giving stilbœstrol. If there is no

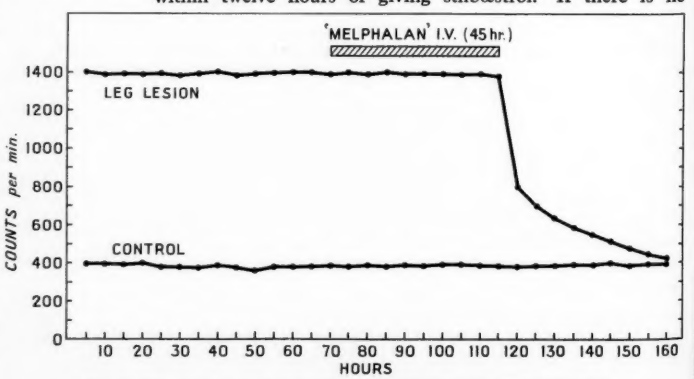

Fig. 5—The response of a malignant melanoma to chemotherapy.

significant change within forty-eight hours the growth is considered to be not œstrogen dependent. Figs. 3 and 4 show a typical response of an œstrogen-dependent tumour to stilbœstrol and testosterone.

Of 26 cases studied, 18 seemed to be stimulated by stilbœstrol and these later responded well to œstrogen-depriving operations or androgens. 3 of these were elderly subjects with atrophic scirrhous growths who would have been treated with œstrogens if the test had not indicated otherwise; they all responded favourably to androgens.

1 postmenopausal case showed striking inhibition of the growth by œstrogens. 7 cases showed no significant alteration in counting-rate after having stilbœstrol for 48 hours or more, and these were classified as not œstrogen-dependent. This was later confirmed by lack of response to hormone-depriving operations or hormone therapy. More cases will have to be studied but the results so far are encouraging.

3. *To Indicate the Response to Chemotherapy*

In view of the increasing use of chemotherapeutic agents for cancer since the technique of marrow storage was developed, it was desirable to know whether this method could be used to indicate response without having to wait for clinical changes to be observed. The possibility of its use as an indicator of tumour response to low dosages of various drugs is at present being considered. If this were possible, one could select the best drug before giving high doses; in view of the frequency of unpleasant side-effects it would be a little comforting to know that the most lethal agent was being used for the tumour. In research this method might prove useful for assessing the response of animal tumours to new therapeutic agents.

Fig. 5 shows the response of a patient with multiple malignant melanomas to *p*-di(chloroethyl)aminophenylalanine ('Melphalan'), given intravenously in a single dose of 100 mg. after splenectomy and marrow storage. One needle probe was inserted into a large lesion on the leg, and another into a control area. The tumour activity fell off strikingly 45 hours after the dose was given. The control showed no significant change. No clinical response to therapy was observed for three weeks, and then the lesions began to regress. The patient came through a period of low white-cell count without complications, and apart from the loss of her hair, she suffered no side-effects. She is now well and leading a normal life, but her case is being regularly followed, because recurrences are likely at any time.

A man, aged 50, with multiple malignant melanomas, was referred after marrow storage and splenectomy for chemotherapeutic sensitivity testing. During the control period, before any drugs were given, the figures fell into a cyclical pattern and so the possibility of the tumour being hormone-dependent was considered. Stilbœstrol 15 mg. t.d.s. was therefore given, and it increased the uptake level of the radiophosphorus considerably. This continued for forty-eight hours until testosterone phenylproprionate, 100 mg. three times weekly by injection, was given instead. The androgens caused striking regression of the melanomatous deposits, and the patient improved. He has been followed up for two months, and is still taking androgens.

Other cases studied to date include lymphosarcoma, Hodgkin's disease, and carcinoma of bronchus with multiple skin metastases.

FUTURE POSSIBILITIES

Much work obviously lies ahead, but at this stage it seems that a reliable machine has been developed for long-continued recording of beta-ray activity from within the body. This has already proved helpful in clinical work, and it may have a place in research. Possible uses might include the following:

To show whether there is any regular cyclical variation in growth activity in other than breast tumours, as in the single case of hormone-sensitive malignant melanoma described above. This has already been suggested in some tumours by the results of animal work, using the technique of repeated biopsy and mitotic counting, and by tissue-culture experiments. If this is confirmed in human tumours of the less radiosensitive kind, it should be possible to select the most responsive time for treatment when radiotherapy is indicated.

To assess the response to radiotherapy of certain inoperable tumours of doubtful radiosensitivity. By means of a tracer dose of radioactive phosphorus and a needle-probe counter inserted into the tumour to be irradiated and a control point, it might be possible to assess the radiosensitivity long before clinical changes can be observed. This might influence the treatment policy in any particular case.

To study the problem of "biologically equivalent dosage" and the effects of fractionation of radiation treatment in human patients.

To measure leakage into the systemic circulation in cases treated by isolated perfusion methods. At the same time it might be used to assess the response of the tumour, or the concentration of a labelled substance in the closed circulation.

In other branches of medicine, where prolonged recording of beta-ray activity from tracers is required—e.g., in problems of blood circulation using chromium-tagged red cells—and for taking readings from organs such as the liver or spleen.

The possibility of using photosensitive crystal-probe counters is being investigated. These would have almost infinite life, and they will be used if their sensitivity can be increased to the required level. It seems likely that this will be achieved.

SUMMARY

A machine has been developed for long-continued recording of beta-ray activity from within human tumours, or other parts of the body, after giving a tracer dose of radioactive phosphorus. It has been put to the following uses:

1. To study growth habits of human breast tumours in vivo.
2. To test hormone dependence of breast tumours so as to select cases for hormone-depriving operations and for hormone therapy.
3. To detect, in vivo, the response of certain human tumours to chemotherapeutic agents before clinical changes can be observed.

My thanks are due to Dr. R. C. Tudway, Dr. Sydney Curwen, and other medical colleagues who have kindly provided cases and given helpful advice; to the department of medical physics of the United Bristol Hospitals, for constructing the machine and for much technical assistance; and to the University of Bristol research committee for financial aid which enabled me to purchase the Geiger probe counters.

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CORTICOSTEROID THERAPY IN CHILDHOOD

SOME children with nephrosis do not respond to high doses of prednisolone, but they do respond to "equivalent" doses of triamcinolone.[1] The most probable explanation for this would be that an adequate concentration of triamcinolone was able to reach the site of the lesion whereas an adequate concentration of prednisolone was not. As it is possible to arrive at an estimate of the mean effective (diffusible) concentration of prednisolone and triamcinolone in plasma from the amount excreted over a known time in the urine (unpublished observations), we decided to investigate this problem.

THE STUDY

Urine specimens from twelve children were kindly supplied by Dr. John Lorber and Prof. R. S. Illingworth of the department of child health, University of Sheffield. The briefest

1. Lorber, J. Personal communication, 1960.

THE URINARY EXCRETION OF PREDNISOLONE (P) AND PREDNISONE AFTER ORAL ADMINISTRATION OF PREDNISOLONE AND INTRAMUSCULAR ADMINISTRATION OF PREDNISOLONE PHOSPHATE; AND THE URINARY EXCRETION OF TRIAMCINOLONE (T) AFTER ITS ORAL ADMINISTRATION

Case no.	Sex	Age (yr.)	Date	Dose (mg.)	Collection time (hr.)	Excretion in urine (μg.)	% of dose	Prednisone excretion (μg.)	Diagnosis and comment
1	F	10	Nov. 11, 1960	P 10	24	P 60	*0·6*	27	Nephrosis
			,, 27 ,,	P 10	24	P 75	*0·75*	40	P 50 mg. given from Nov. 30 to Dec. 19: no response and no moon-face
			Dec. 7 ,,	P 50	24	P 80	*0·16*	25	T began Dec. 20 albumin-free by Dec. 28
			Jan. 12, 1961	P 25	24	P 290	*1·16*	100	Note increased excretion of P during T administration
			,, 26 ,,	P 30	4	P 477	*1·6*	128	
			,, 7 ,,	T 10–15	12	T 6000	?	..	
			,, 27 ,,	T 20	4	T 6250	*31·00*	..	
2	M	6	May 8 ,,	P 120	24	P 215	*0·18*	30	Rheumatic fever and carditis
			,, 9 ,,	P 120	24	P 420	*0·35*	136	No response or moon-face on P
			,, 20 ,,	P-phosphate i.m. 20	6	P 3180	*15·0*	390	Rapid response and appearance of moon-face on T
			,, 25 ,,	T 40	24	T 4550	*11·5*	..	
3	F	10	,, 20 ,,	P-phosphate i.m. 20	6	P 108	?	32	Systemic lupus erythematosus; renal failure
			,, 24 ,,	T 40	24	T 20,000	*50·0*	..	? P-phosphate not absorbed
									No response to P 40 mg. by mouth
									Some response and moon-face on T
									Relapse on dexamethasone
4	F	11	Apr. 13 ,,	P 25	8	P 606	*2·5*	146	Nephrosis early in relapse
			May 13 ,,	T 20	12	T 4800	*24·0*	..	
5	M	8	,, 23 ,,	P 21·5	24	P 70	*0·3*	23	Mild rheumatic fever
			June 14 ,,	P-phosphate i.m. 10	12	P 302	*3·0*	160	
6	F	8	Feb. 2 ,,	P 10	11	P 220	*2·2*	100	Control
7	F	8	Mar. 31 ,,	P 10	11	P 190	*1·9*	47	Mild rheumatoid arthritis
8	M	10	May 26 ,,	P 15	24	P 577	*3·2*	221	Asthma (not ill)
9	F	10	June 5 ,,	P 60	24	P 2400	*4·0*	770	Recovered rheumatic fever
10	F	12	May 24 ,,	P-phosphate i.m. 10	4	P 1123	*1·1*	397	Mild rheumatic fever
11	M	12	June 14 ,,	P-phosphate i.m. 10	24	P 3780	*38·0*	538	Acholuric jaundice
12	M	4	Sept. 5, 1960	T 40	24	T 10,000	*25·0*	..	Panhæmocytopenia

clinical account of these children is given in the table, because a fuller account will be included in a paper by Dr. Lorber.

Prednisolone, prednisone, and triamcinolone were extracted, isolated by paper chromatography, and measured as isonicotinic-acid-hydrazide derivatives. We shall be glad to give the details of these procedures on request.

RESULTS

When prednisolone is taken by mouth in a dose of more than 3 mg. by normal adults, the excretion in the urine is proportional to the dose: when the rate of urine-flow is high about 15% is excreted and relatively little is re-absorbed; when the rate of urine-flow is low about a third of this 15% is reabsorbed. Limited observations of the excretion of triamcinolone in normal adults suggest that 30–40% of an oral dose is excreted unchanged irrespective of the rate of urine-flow.

The table shows that the children excreted 0·16–4% of the dose of prednisolone given by mouth. There was no relation between the amount excreted and the rate of urine-flow, but the flow did not exceed 2·7 ml. per min. in any period. Those children on continuous treatment with prednisolone (cases 1, 2, 3, and 5) had very low levels of excretion, and showed no clinical signs to suggest that they were receiving any prednisolone. By contrast, when triamcinolone was given by mouth a high proportion was excreted and those children who had triamcinolone continuously quickly developed a moon-face.

The low levels of excretion of prednisolone, with the consequent low effective concentration available to the tissues, must have been due to malabsorption, since it is highly improbable that the major pathways of corticosteroid metabolism in children are different from those in adults. To confirm the malabsorption, prednisolone phosphate was given by intramuscular injection to four children. The one of the four who did not excrete a relatively high proportion was seriously ill with systemic lupus erythematosus and gross renal damage. She may not have absorbed all the dose given during the period of urine collection.

So far as absorption is concerned, the difference between cortisone, prednisolone, and dexamethasone on the one hand, and triamcinolone on the other, is one of polarity. Triamcinolone is more water-soluble and less fat-soluble. The severe relapse of case 3 when the therapy was changed from triamcinolone to dexamethasone could have been predicted.

For febrile rheumatic diseases, case 1 (aged 10) and case 2 (aged 6) were changed from high doses of prednisolone, which they were not absorbing, to doses of triamcinolone four to five times higher than we use in adults, *which they absorbed well*. It may be that the giving of these very high effective doses of triamcinolone to children has brought this useful analogue of cortisol into disrepute (see *Prescribers' Journal*, May, 1961). But until such time as we discover how to give prednisolone to children by mouth in a form in which its absorption is reasonably certain it will be better to use triamcinolone.

The findings call for a reappraisal of " corticosteroid " dosage in children. We suggest that in disease states known to benefit from corticosteroid therapy the doses given should be smaller than those found necessary in adults. For instance, in systemically ill patients with rheumatoid arthritis major benefit follows 6–8 mg. a day of triamcinolone, or 10–12·5 mg. of prednisolone (fully absorbed).

CONCLUSION

Prednisolone, and by inference cortisone and dexamethasone, are poorly absorbed by children when given by mouth. In some ill children a very small inconstant fraction is absorbed. Triamcinolone, on the other hand,

is well absorbed and should therefore be given in relatively small doses.

We wish to acknowledge gratefully research grants from the Sheffield Regional Hospital Board and the board of governors of the United Sheffield Hospitals. One of us (H. F. W.) holds a part-time Nuffield Research Fellowship of the University of Sheffield.

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Reviews of Books

Diabetes Mellitus

A Clinical and Pathological Study of 2529 Cases. E. T. BELL, M.D., emeritus professor of pathology, University of Minnesota. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 65. 30*s*.

IN this summary of the life-time experience of an eminent pathologist, the results are simply stated with the aid of many tables, and there is little discussion. Professor Bell has been careful to note the correlation of vascular and other diabetic complications with the duration of the disease, and as far as possible, with the degree of control of the diabetes. He, like others before him, describes the occasional long-term, poorly controlled diabetic who has escaped complications, but in maturity-onset diabetes the main difficulty in making such correlations is the indefinable duration of mild diabetes before the diagnosis is made.

The data comparing diabetics with non-diabetics are interesting. In the author's experience diabetics under 40 years of age with hypertension almost invariably have renal intercapillary glomerulosclerosis. Roughly 1 in 5 diabetics dying at over 40 years had no recognisable histological stigmata of the disease. Professor Bell highlights one of the unexplained findings in some diabetics—namely, the presence of normal granulation of the pancreatic beta cells even when death has occurred in diabetic ketosis. This book can be recommended not only to pathologists but also to clinicians interested in a wide but succinctly written survey of the pathological findings in diabetes mellitus.

The Biochemists' Handbook

Editor: CYRIL LONG, B.SC., D.PHIL., senior lecturer in biochemistry, physiology department, Institute of Basic Medical Sciences, Royal College of Surgeons of England. London: E. & F. N. Spon. 1961. Pp. 1214. 168*s*.

THIS book is the product of collaboration between Dr. Long and his consultant editors, Prof. E. J. King, of the Postgraduate Medical School in London, and Prof. W. M. Sperry, of the College of Physicians and Surgeons, Columbia University, New York. The aim is to present a very wide range of biochemical data, and this is reflected in the index of 63 pages—more than 5% of the total.

There are six major divisions. The first, devoted to chemical data, contains short but clear articles on such subjects as the composition and structure of polysaccharides, manometry, preparation and standardisation of volumetric solutions, chromatography, and electrophoresis. There are divisions on individual enzymes and on metabolic pathways; two others deal with the chemical composition of animal and plant tissues; and one is devoted to physiological and nutritional data (tissue-culture technique, changes of the chemical composition of human blood in disease, chemical composition of foodstuffs, and nutritional requirements).

This is not a textbook, but for each fact stated references are given so that those who want to can proceed further without delay. Considering that this is a handbook of handbooks the price is reasonable.

But is it now profitable to catch " within two covers ", as the publishers pronounce, a vast number of data " which have not previously been collected in this way in the English language "? Anyone who wants to know something about enzymes might do as well with the special books on enzyme chemistry, or if he wants to inform himself on metabolic pathways he will be better served by one of the major textbooks on biochemistry. There are 10 pages on the composition of foodstuffs; but anyone who wants to design a diet will have the appropriate dietary tables anyway. When no other books are available, however, comprehensive handbooks like this are invaluable.

Clinical Disturbances of Renal Function

ABRAHAM G. WHITE, M.D., F.A.C.P., associate visiting physician and chief of the renal-disease clinic, Queen's Hospital Center, Jamaica, New York. Philadelphia and London: W. B. Saunders. 1961. Pp. 468. 73*s*. 6*d*.

THIS book is an informative account of clinical disturbances of renal function by a physician with special experience in renal disease and the physiology of the kidney. There are excellent chapters on glomerulonephritis and pyelonephritis, the nephrotic syndrome, and uræmia. Other sections ably review the relationship of the kidney to hypertension, obstetrics, cardiology, liver disease, and endocrinology. But disorders of acid-base balance in renal disease are inadequately described.

The book gives a predominantly American view of renal disease. Of the 317 references, only 15 refer to work outside the United States, and this is a serious omission in the section on disorders of renal tubular function—a subject in which European workers have made important contributions to knowedge. The account of disorders of the kidney associated with aminoaciduria is often in error: cystinosis is confused with cystinuria, and the specific aminoacid pattern of cystinuria is said to occur in cystinosis and the Fanconi syndrome. Despite these criticisms of detail, Dr. White is to be congratulated on a useful and clear account of renal disease and disordered renal function.

Atlas of Obstetric Technic

J. ROBERT WILLSON, M.D., M.S., professor of obstetrics and gynecology, Temple University School of Medicine, Philadelphia, Pa.; head of the department of obstetrics and gynecology, Temple University Hospital, Philadelphia, Pa. St. Louis: C. V. Mosby. London: Henry Kimpton. 1961. Pp. 294. 93*s*. 6*d*.

THIS atlas is designed to help the young specialist in training and the general-practitioner obstetrician. Dr. Willson contends that the standard obstetric textbooks cannot, for want of space, include detailed descriptions of important manipulations and procedures, so here the management of normal and abnormal labour is set out in a series of excellent illustrations by Miss Daisy Stilwell; and the explanatory text has been reduced to a minimum. The indications and contradictions are discussed briefly, and suitable anæsthetic techniques are described. In view of the increasing popularity of pudendal block anæsthesia, it would be helpful in future editions to have a fuller account of this simple procedure. The very detailed and effective section on forceps rightly emphasises low-cavity and outlet deliveries; and the use of Kielland's instrument is well illustrated and described.

Inevitably in a work of this kind, techniques are described which are not acceptable to all obstetricians, but this does not detract from the book's value. Author and artist have worked closely together to present an admirable account of manipulative obstetrics.

Pathology: a Dynamic Introduction to Medicine and Surgery

THOMAS MARTIN PEERY, M.D., professor of pathology, FRANK NELSON MILLER, Jr., M.D., associate professor of pathology, George Washington University School of Medicine, Washington, D.C. London: J. & A. Churchill. 1961. Pp. 626. 40*s*.

IN the United States, where undergraduate textbooks in medicine have long been growing unwieldy, a reaction towards brevity has of late developed. This volume, exemplifying this

trend, is an epitome of the whole of general and special pathology, in which any rational exposition of the processes of diseases or their underlying ætiological factors has been sacrificed in an attempt to crowd a mass of facts of very varying importance into a sequence of staccato sentences.

In spite of the authors' statement that " the book is planned primarily for medical students ", it is hard to see for what type of reader it will prove appropriate. Any undergraduate beginning pathology will find much of it incomprehensible unless his course is liberally supplemented with lectures and practical work that have been closely correlated with this text. The absence of any diagram or illustration makes the volume of small value as an independent introduction to the subject. More senior students, especially those preparing for multiple-answer examinations, may find it helpful for revision. Others may use it for quick reference; and this use is encouraged by brief bibliographies at the end of each chapter and a notably full index to the text itself.

The presentation of this paperback is uninviting. The text is printed in small type by an offset lithographic process and soon proves fatiguing for the eyes. Because of its substance and format, the book is unlikely to find favour with students in this country.

Cone of Oblivion

L. J. LUDOVICI. London: Max Parrish. 1961. Pp. 216. 25*s*.

FOR as long as scientific discoveries have been made, arguments over priorities have followed. Medical inventions, as much as any others, have been followed by noisy discords. And, since no man can claim a monopoly in inspiration, it is true of most of these controversies that (to quote Sir Roger de Coverley) " much might be said on both sides ".

A notable exception is the unhappy dispute that clouded the introduction of ether anæsthesia, between the Boston dentist, William Morton, and his erstwhile friend, Dr. Charles Jackson. Reviewing their bitter vendetta in a new book, Mr. Ludovici makes it quite clear that the credit for the use of ether in surgery belongs to Morton. Jackson may well have suggested some improvements in the first crude apparatus which the dentist showed him, but he had never even seen a patient anæsthetised until some five weeks after Morton's demonstration. He was, however, clearly subject to a recurrent obsession that other people's ideas (including Morse's concept of the electric telegraph, and Schonbein's discovery of gun-cotton) had been his own.

The feud had a tragic end, for Jackson's unremitting attacks on Morton certainly contributed to the latter's premature death, from cerebral hæmorrhage, at the age of 48. Yet " the whirligig of time brings in his revenges ", and Mr. Ludovici concludes a detailed but easily followed account of this persecution by describing how it was that while contemplating Morton's tombstone Jackson suffered his final mental breakdown. From Mount Auburn Cemetery in Boston he was escorted, patently insane, to the asylum in which he ended his days.

A Prelude to Medical History

FÉLIX MARTÍ-IBÁÑEZ, M.D., professor and chairman of the department of the history of medicine, New York Medical College. New York: M. D. Publications. 1961. Pp. 254. $5.75.

Harvey Cushing, who was a keen student of the works of Vesalius, once organised at a medical convention an exhibit dealing with some aspects of the anatomist's life. The collection of engravings, early editions of the *Fabrica*, and similar relics was placed next to several pharmaceutical stands, and, as Cushing was putting the final touches to his display, a doctor, laden with pamphlets and drug packages, came up and asked for " a sample ". " A sample of what ? " " A sample of your product, of course. Some ' Vaseline ' ! "

Concerned lest any graduate of the New York Medical College might ever subscribe to such an error, Professor Martí-Ibáñez, (who recounts this anecdote) recently organised an elementary course on the history of medicine. His addresses, reproduced in this book, prove that he brought much thought and scholarship to the task. Illustrated by the slides he mentions, these lectures must have been fascinating, and it is a pity that none of his pictures have been reproduced. Purists may cavil at his tendency to talk in general terms, or because no authority or reference is cited for many of his statements. But his enterprise in devising such an interesting introduction to medical history and to medicine itself is greatly to be commended.

Artificial Feeding in Early Infancy

ANDREW BOGDAN, M.D., M.R.C.P.E., D.C.H., assistant in pædiatrics, University of Leeds. Leeds: Tutorial System Publications, Pædiatric Series. 1961. Pp. 24. 3*s*. 6*d*.

THIS booklet by Dr. Andrew Bogdan is written for those working for examinations. It contains what a student should know about artificial foods for infants, their nutritional value, chemical composition, and preparation. It also contains a good deal of information about the average needs of infants. But, although it says it gives only a general outline, it gives little indication as to how this can be adapted to individual needs. It contains old-fashioned feeding tables about timing and measuring feeds, does not discuss the question of demand feeding, and gives little indication of how to deal with feeding difficulties. Many will disagree with its whole approach to the subject and also to some of its statements, such as that during the second twelve hours of life babies are fed on sugar water. On other points it is unfortunately vague. For instance, an examiner who is told that œstrogens inhibit lactation is likely to ask what type of œstrogen and in what dose. The answers are not here. The booklet will be useful as long as it is realised that it covers only part of the subject.

Drugs in the Treatment of Disease (London: British Medical Association. 1961. Pp. 516. 35*s*.).—This book is based on the valuable series of articles published in the *British Medical Journal* from 1958 to 1960. Here they have been brought up to date and grouped together under the different systems so that information about recent advances can readily be found. There are over 60 different contributors, the range of topics is wide, and naturally the degree of critical assessment varies widely. Some of the comparisons of the value of the newer agents with the older remedies are particularly helpful. The prescribing doctor will certainly find this book a useful source of information about the properties and therapeutic use of the many drugs at his disposal.

Anæsthetic Accidents (2nd ed. London: Lloyd-Luke Medical Books. 1961. Pp. 288. 28*s*.)—Changes in anæsthetic techniques and new concepts of the physiology of the body during anæsthesia have led Dr. V. J. Keating to make extensive revisions and additions in this book, which first appeared in 1956. It still deals primarily with the immediate and remote major complications of anæsthesia, and reviews current ideas on their prevention and treatment. As in the first edition, little is said about postanæsthetic vomiting; and because of their serious consequences more space might have been given to vomiting and regurgitation during anæsthesia. There are surprisingly few references to the use of halothane, considering its potency and now widespread use. A dangerous electric defibrillator is described, and even the isolating transformer recommended would not make it safe. The naming of drugs is inconsistent, both trade names and approved names being used. But apart from these points the book is excellent.

Advances in Thyroid Research (Oxford: Pergamon Press. 1961. Pp. 537. 126*s*.).—This volume, under the general editorship of Dr. Rosalind Pitt-Rivers, is the transactions of the Fourth International Goitre Conference, held in London in July, 1960. It contains the address by the president, Sir Charles Harington, and nearly all the papers on the conference programme. They fall into several main groups: biochemical and physiological, genetical, immunological, epidemiological, and clinical. These varied approaches give the reader a comprehensive picture of the areas in which progress is being made, but he needs to have enough previous knowledge of the subject to identify the significant contributions.

THE LANCET

LONDON 12 AUGUST 1961

"Euthanasia"

MANY in medical practice must know what it is to have charge of a patient with a relentless disease which makes its victim completely and perhaps painfully powerless—dependent from moment to moment, day and night, on others; unable, it may be, to speak understandably, to wipe the nose, to put food or drink to the lips. For this condition there is no remedy but death, and patient or spouse may ask "how long?" and whether life cannot be ended. Often the doctor must wish he could call in Death, the "gentle" or "kindly" death of Elizabethan poets (who knew ungentle death better than we do); but Death is not in sight or within call. Yet ought a doctor not to have something to offer? If the law permitted, would he himself willingly end the useless, burdensome, perhaps painful life? Does he in his heart approve of the law? If not, how would he have it altered?

Compared with permanent helplessness, the problem of a painful final illness, with the patient "dying hard" or too slowly, is usually less troubling; for Death is in sight. Almost certainly something can be done at least to reduce, if not abolish, each particular pain or discomfort; no qualm need be felt about the possible life-shortening effect of any pain-relieving remedy; there is no fear of addiction, because the patient is going to die; and some sort of answer can be given to the agonised "how long?". Here the doctor has no such sense of impotence, for he can *act* in many different ways; and he will seldom feel that the law curtails his power to help his patient. Yet it is this second type of case that seems most to trouble the public mind, and it is for this type that the Euthanasia Society—in a pamphlet [1] bearing a most impressive list of approvers—pleads for an alteration in the law. By this alteration, people likely to die "in the not distant future" could apply to have their lives painlessly ended—obtaining such permission very much as permission for cremation is obtained now. Euthanasia being authorised, "it could be carried out either by the patient's own doctor if he so desired, or by a medical man authorized to do so by the Minister".

Written moderately and persuasively, this appeal states and answers fifteen likely objections. But if we agree that some of these have little weight, others surely are given less than their due? Courageously quoting the opinion of the late Dr. HARRY ROBERTS that doctors are perhaps the least enthusiastic advocates of euthanasia—"not from lack of sympathy, but because they know better than does the public the sinister possibilities attendant on the giving of increased license to the less-reputable members of their profession" [2]—the authors of the pamphlet reply by questioning whether doctors are in fact the best judges in this matter. What cannot be disputed, however, is that doctors are very deeply involved. Under the proposed arrangements the applicant is to begin by "talking the matter over frankly with his doctor", which implies that the doctor will at least be asked whether or not he thinks his patient's life should be ended. Next there is the apparent assumption by every advocate of "euthanasia", lay or medical, that a medical man will do the painless killing; and even the suggestion that but for the law he would do it quite willingly. But would he? There is, for the agent if not for the subject, a very real difference between shortening life, when this is a price that has to be paid for the relief of suffering, and deliberately, conclusively, killing with a lethal drug—even though this is "perhaps no more than a hypodermic injection". How general is this feeling is well shown by the euphemisms employed when pet animals are put to sleep, put away, or (hardening the heart) put down; and the pamphlet similarly speaks of how the terminator of life "carries out euthanasia" and "gives help in terminating misery" or "in meeting his patient's request". The reality, however described, would often be profoundly disturbing. Yet the taking of life, once licensed, might seem to be a duty owed by his doctor to the requesting patient; or, if many practitioners declined it, a class of "medical men authorised by the Minister", and presumably earning a fee, might arise—a peculiarly repugnant thought. Giving hypodermic injections demands little skill, and one is tempted to ask whether all the people who endorse this appeal would be ready, if authorised, to "give help" of this particular kind. If not, should they consider more precisely what they are demanding of the medical man and medical profession?

Moreover, if some procedure for taking life were established, there might be other and graver consequences. In his recent study, EXTON-SMITH [3] found that unrelievable enduring pain and misery is worst not, as the public suppose, among patients dying of cancer, whose pain, if present, he found controllable and relatively short, but in the victims of locomotor disorders not essentially lethal. If "euthanasia" is granted to the first class, can it long be denied to the second? Some may think they have the better right. But if they are given it, what of the very many others whose lives are useless, burdensome to themselves, their relatives, and the community, unhappy if not painful, unlikely to end soon, and who, for one of many possible reasons, will not be applicants for voluntary euthanasia? Each step is so short; the slope so slippery; our values, in this age, so uncertain and unstable. To many it must seem unwise to take this first step which could count for so much; yet we may be pressed, as a profession, to agree to its being taken. Individually and collectively we should at least be sure where we stand.

But if we think legalisation of induced euthanasia

1. The Case for Voluntary Euthanasia. Obtainable from the Euthanasia Society (president, the Earl of Listowel; chairman, Dr. Leonard Colebrook, F.R.S.), 13, Prince of Wales Terrace, London, W.8.

2. Roberts, H. Euthanasia and Other Aspects of Life and Death. London, 1936.

3. Exton-Smith, A. N. *Lancet*, Aug. 5, 1961, p. 305.

undesirable, we might still press harder for extension of means towards euthanasia in its derivative sense—" an easy, happy death ". The pamphlet here reviewed, EXTON-SMITH's study, and GLYN HUGHES' survey [4] all show the gross inadequacy of our provision for decent, seemly quitting of life, with relievable pain and distress relieved and comfort given; while CICELY SAUNDERS' *Care of the Dying* [5] (which all should read, and which advocates of induced euthanasia should specially study and consider) shows in detail and from experience what can be done, and shows too that " to make a good end " is not an entirely outworn conception or accomplishment. If euthanasia, in this sense, were put on a par with, say, safe childbirth; if the known means to make death, when it comes, easy and happy were applied by individual and collective effort with intelligence and energy, could not all but a few deaths be made at least easy and, in our ageing population, even happy? And should we not avoid this pressure to assume the right—even the duty—to take life, with all the implications and consequences that assumption carries?

Green for Danger

THE progress of the past decade against the common gram-positive infections has left in its wake some disturbing whirlpools of activity by lesser organisms. The danger of emergence of coliform infection, foreseen by MILES [6] in 1944, and defined by FLOREY et al.,[7] was at first mitigated by streptomycin and the broad-spectrum antibiotics; and it has long been dwarfed by the problem of drug-resistant strains of *Staphylococcus aureus*.[8 9] Nevertheless, there is clear evidence [10 11] that, since about 1950, the steady rise in the incidence of infection in hospitals has been marked by prevalence of an unmanageable family of gram-negative bacilli, not only in wounds and burns as in former days, but also in lungs, blood-stream, and meninges. Reports in the past two years [12 13] indicate that the latest, certainly the most colourful, and possibly the most intransigent, upstart in this family is *Pseudomonas pyocyanea*. Unlike some other entries in the field of hospital infection, *Ps. pyocyanea* arrives with a notorious reputation for survival in unlikely situations; for resistance alike to antiseptics, physical agents, and antibiotics; and for easy visibility, ready growth on culture, but strong resistance to elimination. Apparently its only virtue was its comparative lack of pathogenicity; but reports have been accumulating that in young or debilitated patients it causes severe infection which, in the meninges or blood-stream, is usually lethal.[14–16] This development may not yet be widespread, but it is portentous; and a detailed review by CURTIN et al.[17] of 91 episodes of *Ps. pyocyanea* bacteræmia is timely.

These 91 episodes occurred in 88 patients, of whom 73 died. The majority were children, mostly with predisposing factors such as prematurity (18), congenital defects (13), or acquired disease (31)—including 17 with leukæmia. Most of the 26 adults were elderly patients with bladder disease, malignant neoplasms, or other debilitating conditions. The portal of entry was not always obvious; but the skin (including the umbilical stump in 4 infants), intestine, ear, and urinary tract (especially after instrumentation) were all identified as likely sites. In several cases there was no demonstrable portal of entry. On 10 occasions the bacteræmia was transient, and 4 patients recovered without antibacterial therapy. Most of the patients had already received one or more antibiotics; and in 22 instances bacteræmia developed as a superinfection during antibiotic therapy. The presenting features did not differ from those in other forms of bacteræmia; and supposedly characteristic manifestations, such as ecthyma gangrenosum and Shanghai or " typhoidal " fever, were lacking in all but 2 cases. The effectiveness of treatment in this series is not easily assessed, partly because a variety of drugs and combinations of drugs was administered, and partly because the outcome depended largely on the nature of the underlying disease. Apparently results were best when polymyxin B was used in combination with streptomycin; in 5 out of 9 assessable cases, polymyxin B seems to have been effective when given alone; streptomycin alone was ineffective. The in-vitro sensitivity of the individual strains is not analysed, but apparently 13 out of 31 cases treated with tetracycline and/or chloramphenicol responded favourably—though 9 of these patients also received streptomycin or polymyxin B or both. In 2 cases antibiotic therapy was ineffective until surgical drainage had been performed. This useful survey shows that severe infection with *Ps. pyocyanea* is confined to patients rendered vulnerable by a predisposing lesion, and that infection " is almost invariably associated with diminished resistance in the host and occurs in an environment favourable to infection—the hospital ". Patients in this category already receiving antibiotics are especially vulnerable; for undoubtedly imbalance of the normal bacterial flora, especially in the intestine, favours access of *Ps. pyocyanea* and other facultative pathogens.

Ps. pyocyanea often contaminates dressings and instruments because it can resist standard concentrations of certain antiseptics, and other disinfecting measures; it may actually grow in cetrimide, and in ophthalmic departments catastrophic incidents have followed the use of contaminated bottles of this antiseptic. But, hardy as it is, the organism can be eliminated by closing and disinfecting the ward and its contents. The real problem arises when *Ps. pyocyanea* is in (as opposed to on) the patient, whether through spread from a superficial focus or following lumbar puncture, catheterisa-

4. Glyn Hughes, H. L. Peace at the Last. (Published by the Calouste Gulbenkian Foundation, 3, Prince Albert Road, London, N.W.1.) 1960; see *Lancet*, 1960, ii, 195.
5. *Nursing Times* Reprint. Macmillan & Co. Ltd., St. Martin's St., London, W.C.2. 2s. 6d.
6. Miles, A. A. *Lancet*, 1944, i, 809.
7. Florey, H. W., Ross, R. W. N. L., Turton, E. C. *ibid.* 1947, i, 855.
8. Barber, M. *J. Path. Bact.* 1947, **59**, 373.
9. Rountree, P. M., Thomson, E. F. *Lancet*, 1949, ii, 501.
10. Finland, M., Jones, W. F., Barns, M. W. *J. Amer. med. Ass.* 1959, **170**, 2188.
11. Barber, M. *J. clin. Path.* 1961, **14**, 2.
12. Williams, R., Williams, E. D., Hyams, D. E. *Lancet*, 1960, i, 736.
13. Sussman, M., Stevens, J. *ibid.* 1960, ii, 734.
14. Asay, L. D., Koch, R. *New Engl. J. Med.* 1960, **262**, 1062.
15. Kwantes, W. *Mon. Bull. Min. Hlth Lab. Serv.* 1960, **19**, 169.
16. Clifford, H. E., Stewart, G. T. *Lancet*, July 22, 1961, p. 177.
17. Curtin, J. A., Petersdorf, R. G., Bennett, I. C. *Ann. intern. Med.* 1961, **54**, 1077.

tion, or other procedures: if the organism gains access to the blood-stream, nervous system, or eye,[18 19] it is peculiarly destructive and is often found to be resistant to the usual antibiotics. Polymyxin B is generally regarded as the antibiotic of choice, though it is by no means uniformly successful and it may be toxic.[20 21] CLIFFORD and STEWART [16] have suggested that a new methane-sulphonic acid derivative of polymyxin B may be equally active and is probably non-toxic, enabling it to be used intraventricularly or intrathecally in large doses in the treatment of meningeal infection. There are also encouraging reports [22 23] about 'Colistin' (colymycin), a mysterious Japanese antibiotic similar in its properties to a polymyxin and also used in the form of the methane sulphonate. *Ps. pyocyanea* is susceptible to phage activity, but stock or pooled phages have proved of no avail in treatment; French workers [24] claim that phages isolated along with the infecting strain can be selectively adapted for therapeutic application in the individual case. At present therapy should include polymyxin B, preferably in the form of the new derivative, together with any other antibacterial agent to which the infecting strain is sensitive; and, whenever possible, infection should be eradicated from local sites by topical applications or surgical drainage.

Eradication of systemic infection with this organism remains a formidable chemotherapeutic problem. The identification in hospital of even a single case of *Ps. pyocyanea* infection calls for instant alertness and determined prophylaxis.

Treatment of Scoliosis

IN the early days of orthopædics, correction and prevention of deformity depended on skilful splinting. Later, with the rise of antiseptic and aseptic surgery, surgical procedures were increasingly used to correct severe deformity, but splinting was the main weapon for the prevention of deformity; and, especially in poliomyelitis and tuberculosis, the early workers achieved outstanding results in preventing deformities of the limbs, though they were less successful in preventing severe spinal deformities, whether these were due to tuberculosis, poliomyelitis, or an inherent growth defect.

Several factors have contributed to a new outlook. In the first place gross deformities have largely disappeared from the hospitals of the more developed countries. Secondly, it has come to be realised that the successful prevention of the more severe deformities depends on really early diagnosis: for instance, the pioneer work of VON ROSEN and, in this country, BARLOW showed that if congenital dislocation of the hip is diagnosed in the neonatal period a good result can be obtained in almost every case by simple measures such as splinting the hips in abduction. Congenital dislocation of the hip is usually primarily a disorder of the soft tissues, and any deformity of the bones is secondary; therefore correction of the joint deformity at an early age nearly always leads to normal growth of the bones. The same is probably true in talipes equino varus, where the bones will develop normally provided the joint deformity is fully corrected at an early age. Here, many of the bad results have been due to the fact that the joint deformity was not fully corrected; often there was only apparent or compensatory correction—for example, over-correction at the tarsometatarsal joint might mask failure of correction at the subastragaloid and mid-tarsal joints. If the bones are to grow normally the affected joint must be fully corrected at an early age; this must be a true correction; and it must be obtained without damage to the bones, which forcible manipulation often causes. Radiographs must be taken; and in most cases tight muscles, ligaments, and joint capsule must be divided at an early age.

In scoliosis the matter is still more complex. In the fully developed scoliotic spine there is not only deformity of joints but severe deformity of the bones themselves, ultimately due to considerably greater growth of the bone on the convex side of the curve. In certain types of congenital, infantile, and so-called idiopathic scoliosis, an intrinsic growth disorder of the spine is a primary feature. In scoliosis secondary to poliomyelitis, subluxation of the intervertebral joints probably precedes and leads to the abnormality of bone growth. But, whatever the primary cause, ultimately there is severe growth imbalance. For more than a century and a half, efforts have been made to control this imbalance conservatively; such treatment, although it succeeds in the milder cases and often produces considerable apparent improvement by increasing the compensatory curves, has not usually controlled severe progressive curves with an intrinsic growth imbalance or corrected established thoracic curves.

In the past ten years some surgeons have tried to control scoliosis by early operation; and MUSTARD [1] has recorded his experience with 160 children who had correction and fusion in the growing period. In favourable curves—i.e., in the lower thoracic and upper lumbar regions—posterior fusion will lead to arrest, and in some cases improvement, if it is undertaken soon enough. A slightly different principle of controlling spinal growth in the young by epiphysiodesis has been used by ROAF,[2] and in young patients this procedure will lead to correction with growth instead of the otherwise almost inevitable deterioration. The difference between the success of such measures nowadays and their failure thirty years ago is due partly to improvements in anæsthesia, blood-transfusion, and resuscitation,[3] which have made operations on children safer. GARRETT et al.[4] in California have shown that even patients with very severe respiratory paralysis can undergo extensive operations without excessive risk. Prophylactic surgery to prevent progressive deformity, and in some cases to restore normal alignment, can

18. Botterell, E. H., Magner, D. *Lancet*, 1945, i, 112.
19. Stanley, M. M. *Amer. J. Med.* 1947, **2**, 347.
20. Brownlee, G., Bushby, S. R. M., Short, E. E. *Brit. J. Pharmacol.* 1952, **7**, 170.
21. Trapnell, D. H. *Lancet*, 1954, i, 759.
22. Wright, W. W., Welch, H. *Antibiot. Annu.* 1959–60, p. 61.
23. Meleney, F. L., Prout, G. R. *Surg. Gynec. Obstet.* 1961, **112**, 211.
24. Bertoye, A., Courtieu, A. L. *J. Méd. Lyon*, 1960, **41**, 739.

1. Mustard, W. T. *Canad. med. Ass. J.* 1961, **84**, 1358.
2. Roaf, R. *J. Bone Jt Surg.* 1960, **42B**, 40.
3. Moe, J. H. *ibid.* 1961, **43A**, 471.
4. Garrett, A. L., Perry, J., Nickel, V. I. *ibid.* p. 474.

now be safely practised in progressive spinal deformities such as scoliosis. Possibly, as in club-foot, the need for extensive operation on bone may be obviated by full correction at a very early age, if necessary by division of muscles and ligament; but such surgery is only justifiable if it is based on early and accurate diagnosis and knowledge of prognosis. In a changing world one requirement has not changed—namely, good surgical judgment, which still consists largely in knowing when to be bold and when to be cautious.

Annotations

AUGMENTED ROMAN ALPHABET

THE first reaction to a paragraph in the experimental augmented Roman alphabet [1] is likely to be that it is graceless—no capitals and nineteen funny-looking new letters among twenty-four old ones (few will regret the loss of q and x). It is nevertheless easy to read, though the 1000 children in the research project announced by the Institute of Education of the University of London may not have such a straightforward time as their contemporaries reading the " old " alphabet. At least three years must elapse before we know the results of the experiment, which has many implications for those interested in changing human behaviour.

Fluent reading and acceptable spelling involve highly complex skills, from controlled movements of the eyeballs to discrimination of patterns and the use of symbols or code. For most of us a blessed amnesia covers the agony or tedium we went through in mastering these skills, and only when we hear of a child failing to get to grammar-school through inexplicable disability in reading, or when we see the spelling of some applicants for secretaryships or medical-school places do we realise that these skills are not to be taken for granted. Not everyone can learn them; between 1 and 4% of 11-year-olds cannot read beyond 7-year-old level and very many more are only semiliterate.

Though the causes of specific reading disability are various and interwoven, for many children an important one is the irrational English spelling. A single word may be presented as several different visual patterns—e.g., AND, And, and, &, in plain print, with written variations galore. A single speech sound may be spelt in several ways—e.g., the sound common to hoe, though, oh, show, yolk, and sew. A single group of letters may represent several speech sounds, as in bone, gone, done, one. There are thus innumerable inconsistencies between meaning, word, visual pattern, and auditory pattern; chaotic instead of regular relationships have to be learnt. It is this difficulty which sponsors of the augmented Roman alphabet propose to tackle, providing an alphabet of 43 letters, each standing for one sound and one sound only. The aim is not to reform English spelling (though some may hope it will facilitate this), but to provide a special alphabet on which children can learn to read, transferring at the age of 7 or so to what is good (or bad) enough for their elders.

Here and there over the past hundred years a courageous and ingenious teacher has tried such a thing (often with success), but this is the first ambitious attempt to study the long-range effects with adequate controls. The experiment is sponsored by the University of London Institute of Education and the National Foundation for Educational Research. It affects 1000 children who will start in September to learn to read it in twenty-four schools in Staffordshire, Harrow, and Oldham; it affects their parents, whose cooperation is needed; it affects some 80 teachers who have to be specially trained; and it involves the transcribing of 200 books. Whatever its outcome, such an ambitious project is bound to produce useful information on the processes involved in learning to read.

We know little about the best conditions for learning to read. In education, as in commerce, we should see just how, when, and where, expenditure gives the best returns, and whether the byproducts are good or bad. If the laws that govern spelling were rational and not erratic, a lot of mental energy would surely be freed for more useful learning, and the byproducts might be much better. It is unlikely that impressing upon the child the need to conform to incomprehensible spelling rules is the best way to teach him the advantages of reasonable law and order. In this experiment, therefore, it might be worth looking at other kinds of mental progress as well as skill in reading. But the research-workers may well have plenty to do without going into such complexities, and we wish them well in their imaginative enterprise.

1. See *Times*, July 18, 1961.

DIAGNOSIS OF ANGINA PECTORIS

MANY patients with angina pectoris do not describe classical and diagnostic pain: angina may come on at rest as well as with exercise; stooping may aggravate the pain; or the site of pain may be atypical. The maligned television set sometimes provides a diagnostic clue: pain brought on by an exciting boxing-match or a gory Western is true angina, as was John Hunter's pain induced by his coachman's thieving.

A reliable objective test would obviously be of great value in diagnosis, especially as the electrocardiogram (E.C.G.) at rest is normal in 40–50% of these patients.[1] The effect of exercise on the E.C.G. has been widely used in diagnosis. Such an exertion test is safe for patients with a normal E.C.G. at rest and with no recent long-continued pain suggesting myocardial infection; the exercise must be closely watched by a doctor. Master and his colleagues have since 1929 developed a standardised exertion test.[1 2] They prescribe a set number of journeys up and down two 9-in. steps, according to age, sex, and weight. In only 3 of 100 cases of angina did this test provoke so much pain as to stop the exercise.

Most British physicians, including Wood et al.,[3] test their patients under careful supervision with maximal rather than standard exertion. The patient exercises on any convenient stairs until chest discomfort, dyspnœa, or fatigue develops. ST depression of more than 1 mm., remaining flat or sloping downwards for more than 0·08 seconds, is abnormal. A depressed but upward sloping ST segment is of no significance. Occasionally only T-wave inversion develops.[4] Wood et al. found such a positive exertion response in 88% of patients with angina but in only 1 of 100 healthy controls.

The E.C.G. response to exertion is too variable from day to day for it to be of value in assessing drugs administered

1. Master, A. M., Rosenfeld, I. *N.Y. St. J. Med.* 1961, **61**, 1850.
2. Master, A. M., Oppenheimer, E. T. *Amer. J. med. Sci.* 1929, **177**, 223.
3. Wood, P., McGregor, M., Magidson, O., Whittaker, W. *Brit. Heart J.* 1950, **12**, 363.
4. Robb, J. P., Marks, H. H., Mattingly, T. W. *Trans. Ass. Life Insce med. Dir. Amer.* 1956, **40**, 52.

to provide sustained relief of angina. (Moreover pain may be relieved while E.C.G. changes of ischæmia persist.[1]) For such treatment monoamine-oxidase inhibitors [5] and pentaerythritol tetranitrate [6] have been proved useless. Fortunately, at least half these patients improve with a placebo prescribed with enthusiasm and interest [5]; so both patient and doctor need a drug they can believe in, even if it does not really work.

THE UNMARRIED MOTHER AND HER CHILD

UNLESS it gets financial help, the National Council for the Unmarried Mother and Her Child will soon have to reduce its activities to a much smaller scale.[7] Yet, except for the periods during and immediately after the world wars, more illegitimate babies are being born now than at any time in the past eighty years. Every year the figure increases, both absolutely and as a percentage of total births. Formed in 1918, when the illegitimacy-rate in England and Wales, at 6·3%, was the highest for fifty-five years, the Council has ceaselessly worked for legislative reform, especially in connection with the Bastardy and Affiliation Acts, and has kept a close watch on all legislation likely to affect the illegitimate child. It is largely through its efforts that in the past forty years the legal position of the illegitimate child has been so much improved.

Similarly, the interests of unmarried parents and their children have been watched on an administrative plane. The Council does what it can to encourage local authorities to make full use of their powers for the care of mothers and children. It tries to promote and encourage hostels, homes, and other suitable accommodation to meet the varying needs of mothers and babies throughout the country, with the special aim of making it possible to keep mother and child together. Though most individual cases are dealt with by local authorities and welfare workers, the Council also has a department which deals with individual inquiries, and many thousands have been helped. At the moment there is a particular need for accommodation for unmarried mothers, both before and after their babies are born, and the Council would like to hear from anyone who would be willing to provide such accommodation, on a reasonable business basis. In addition, the Council tries to inform the public by speeches, through the press, and in every way it can, about the needs of the illegitimate child. It has had much to do with the recent publication of *The Unmarried Mother and Her Child*, by Virginia Wimperis, a comprehensive, scholarly, and highly readable study of the British problem in relation to the problems and methods of attacking illegitimacy in other countries.[8]

Though the legal rights of the illegitimate do not now differ greatly from those of the legitimate child, he is still at a disadvantage. Infant mortality is greater in the illegitimate than in the legitimate (in England and Wales in 1959 it was 27 compared with 22), and the proportion born prematurely is higher than normal. Both breast-feeding and attendance at welfare centres are less frequent in these children, whose physical wellbeing, nutrition, and growth has been described as " often far below that of their legitimate contemporaries ".[9] They also have a higher accident-rate: in the Newcastle Survey [10] 18% of the illegitimate babies suffered accidents in their first year against 5% of the rest. Of increasing importance at present is the problem of illegitimate pregnancies in teenagers. This is of the utmost concern to the Council, who are in a position to assess its significance against a background of allied problems such as sexual promiscuity and juvenile delinquency.

Apart from a small Ministry of Health grant (£1250 per annum) and small grants from local authorities, the Council depends entirely on private donations and subscriptions. During the year ended last March it had a deficit of over £3500, which had to be met by selling some of its few investments. It will be a real loss if its activities have to be drastically curtailed just at a time when they seem to be particularly needed. Its address is: 255, Kentish Town Road, London, N.W.5.

LUNG ABSCESS

THE results of treatment of lung abscess still leave much to be desired. Purposeful management [11] is no less necessary now that antibiotics are available. Fifer et al.[12] have analysed 55 cases of primary lung abscess treated in one or another of four large teaching hospitals in Minnesota in 1952-56. Of 51 cases treated medically (4 were treated surgically " before adequate medical treatment had been given ") 28 had a successful outcome and 22 did not; in 1 case the data were inadequate for a conclusion. (" Success " and " failure " are defined chiefly in terms of radiographic clearing and subsequent continued good health.)

The factors which Fifer et al. found to be unfavourable were delay in starting therapy, the presence of a large abscess cavity (over 37 sq. cm. on a chest radiograph), fever continuing beyond three weeks, irremediable bronchial disease such as bronchostenosis, the coexistence of diabetes mellitus, and inadequate or improper antibiotic treatment. Alcoholism was by far the commonest predisposing factor in the series, in which 20 cases were due to alcoholic stupor; but the prognosis in alcoholics was found to be as good as in others.

Commonly by the time patients are referred to hospital they have already had some form of antibiotic treatment, but seldom with any prior examination of their sputum. Proper bacteriological diagnosis may then be difficult or impossible. Reviewing the bacteriological findings and the antibiotic therapy of 52 of their patients, Fifer et al. found that gram-negative bacilli were present in 23 and pathogenic staphylococci in 18. Pneumococci were present in 8 and streptococci in 8. In earlier studies streptococci were the most commonly recovered organisms, and the present figures perhaps reflect the general trend towards increased prevalence of antibiotic-resistant organisms. 34 patients had lesions due to virulent gram-negative bacilli, coagulase-positive staphylococci, or both. Treatment failed in 3 out of 8 cases where such staphylococci were present, and in 8 out of 19 cases with gram-negative bacilli. In 2 cases both types of organism were present.

The average duration of drug treatment was five weeks in medically treated cases and seven weeks in surgically

5. See *Lancet*, 1961, i, 150.
6. Phear, D., Walker, W. C. *Brit. med. J.* 1960, ii, 995.
7. Forty-first report of the Council: May, 1960, to March, 1961.
8. See *Lancet*, 1961, i, 380.
9. Cooper, C. " The Illegitimate Child ", reprinted by the N.C.U.M.C. from the *Practitioner* of April, 1955.
10. Spence, J. C., Walton, W. S., Miller, F. J. W., Court, S. D. M. A Thousand Families in Newcastle upon Tyne. London, 1954.
11. Brock, R. C. Lung Abscess. Oxford, 1952.
12. Fifer, W. R., Husebye, K., Chedister, C., Miller, M. *Arch. intern. Med.* 1961, **107**, 668.

treated cases. Penicillin was effective in only two-thirds of the cases. In 21 of the 28 successfully treated patients, intravenous penicillin had been used.

Perhaps the most thought-provoking observations in this report arise from the analysis of the 22 cases in which medical treatment failed. According to the criteria used, 11 of these patients had received inadequate or improper antibiotic therapy—for example, administration of penicillin in gram-negative infections. 5 others did not respond because a combination of resistant organisms was present. These unsatisfactory results are set against the successful outcome in 20 out of 24 cases in which " correct " therapy was applied—which illustrates the paramount importance of critical bacteriological control.

Surgical treatment was undertaken in 16 of the 55 patients, usually, though not always, after medical treatment had failed. External drainage was performed in 5 cases, always with unsatisfactory results; and Fifer et al. suggest that this procedure has little place except among patients in whom medical treatment has failed and who are too ill for lung resection. Though lung resection is such a satisfactory form of treatment (only 2 failures in 11 cases) this may not always be necessary when cavities fail to close on antibiotic treatment, for " late closure " occurred in 12 out of 19 patients who on discharge from hospital still had cavities after antibiotic therapy.

In general, Fifer et al. condemn external drainage but advocate lung resection, and they emphasise the need for close bacteriological control. Where these precepts were observed three-quarters of the patients recovered satisfactorily. Where they were not observed, treatment failed in three-quarters of the cases. Few will disagree with the plea, implicit in this conclusion, for greater diagnostic accuracy in dealing with cases of primary lung abscess in medical and surgical wards alike.

THE DAY THE DAM BURST

NOTHING resembling the panic described by James Thurber occurred in Worksop when the bottom fell out of the main water reservoir.[1] The bottom was of old concrete (and poor at that) and quite suddenly a hole 6 ft. × 4 ft. appeared over an underlying fissure in the soil through which the water disappeared faster than it could be pumped in. The water engineer took immediate steps to plug the leak, but these were unsuccessful and thereafter the water was pumped straight from the boreholes into the mains. With the help of an auxiliary supply from a neighbouring colliery this ensured a supply to most of the town, but pressure was too low in the higher parts, which had to be supplied by water-carts.

The responsibilities of the medical officer of health were heavy. The chlorinators at the main pumping-station refused to work satisfactorily at the higher pressures, and in one part of the town presumptive coliform counts of 30–160 organisms per 100 ml. were found. The level of chlorination was raised from 0·4 p.p.m. to 2·0 p.p.m., and while there were few complaints about the taste there were a good many about the death of goldfish. A more alarming observation was the fluctuation in the level of chlorination (from 1·6 p.p.m. to nil) within a few hours in those parts of the town supplied from the colliery. This fault too was traced to chlorinators—this time in the colliery supply—which failed under pressure. Whether the consumer received chlorinated water or not depended on the relative pressures in the two sources of supply. Daily samples of water were taken for bacteriological examination, and, with the horrid story of the Croydon accident of 1937 in mind,[2] all the men engaged in repair work were examined to detect a typhoid carrier—without result.

There are some lessons here for everyone. The late Sir William Savage used to preach that every medical officer of health ought to turn over in his mind from time to time what he would do in the face of a whole variety of unexpected disasters. The health department at Worksop seems to have acted promptly and efficiently, and, as Dr. McCann points out, this accident underlines once again that medical responsibility for clean water is not limited to what comes out of the tap. The chlorinating plants, efficient no doubt for years past, failed when subjected to unusual pressures. We are all inclined to accept as efficient machinery which we do not fully understand. The general experience with autoclaves in hospitals shows how wrong we are.

PSEUDOXANTHOMA ELASTICUM

ALTHOUGH the lesions attributable to pseudoxanthoma elasticum may be widely distributed through the tissues and organs of the body, it is more commonly recognised by dermatologists and ophthalmologists than by general physicians. The disorder of the skin is characterised by laxity at flexures and accentuation of creases, which give it an appearance resembling that of Moroccan leather.[3] The name pseudoxanthoma is derived from the peculiar yellow macules or plaques in the affected areas. In well over half these patients retinoscopy reveals a peculiar brown or grey streaking resembling vessels in distribution but not in colour; hence the term angioid streaking. Apart from the risk of blindness due to these retinal changes, the most serious manifestations of the disease result from degeneration of the muscular arteries of the viscera and the extremities. The changes in these vessels may lead either to progressive obliteration, with symptoms such as angina pectoris and intermittent claudication, or to dilatation with aneurysm and hæmorrhage.

Despite considerable study of the affected skin by histology, chemistry, and electron microscopy, the nature of the underlying lesion is undecided. Investigators cannot even agree whether collagen[4] or elastin[5] is primarily affected. The following observations have all been advanced in favour of a primary defect of collagen: the quantity of elastin in the skin is too small to account for the histological changes; the arteries usually affected are of the muscular type in which the media is almost devoid of elastin but rich in collagen, and the internal elastic lamina in the affected vessels usually appears normal; and electron microscopy of the skin lesions reveals abnormal fibres with the characteristic 640 Å banding of collagen.[6] The only evidence strongly supporting a primary defect of elastin is the positive staining of the affected fibres by the methods usually regarded as specific for this material, and the digestibility of these fibres by the enzyme elastase. But investigations on

1. McCann, M. B. *Mon. Bull. Min. Hlth Lab. Serv.* 1961, **20**, 122.
2. See *Lancet*, 1937, ii, 1257, 1319.
3. McKusick, V. A. Heritable Disorders of Connective Tissue; p. 215. St. Louis, 1960.
4. Hannay, P. W. *Brit. J. Derm.* 1951, **63**, 92.
5. Moran, T. J., Lansing, A. I. *Arch. Path.* 1958, **65**, 688.
6. Tunbridge, R. E., Tattersall, R. N., Hall, D. A., Astbury, W. T., Reed, R. *Clin. Sci.* 1952, **11**, 315.

elastotic degeneration of collagen fibres [7 8] have shown the unreliability of both these methods for differentiating between these two types of connective-tissue fibre.

The familial occurrence of pseudoxanthoma elasticum provides clear evidence of a genetic transmission, and the absence of overt disease in the parents of affected subjects, together with the increased prevalence of the disease in the offspring of consanguineous marriages, may be regarded as indicating the action of a recessive gene.[8] The most convincing evidence of the recessive nature of any gene is the finding of incomplete expression of the gene in some of the clinically normal relatives of affected subjects. For this reason a report by Berlyne, Bulmer, and Platt [9] is an outstanding contribution to the genetics of the disease. In the 3 affected families on which their study was based, 9 of 22 apparently unaffected relatives showed an abnormality of the retina characterised by unusual visibility of the choroidal vessels. A further peculiarity to which Berlyne et al. call attention is the large proportion of families in which the disease is confined to one sex—namely, 6 families with only males affected, 15 families with only females affected, and only 1 family with both sexes involved. These figures strongly support the hypothesis that the responsible recessive gene is partially sex-linked—that is, it resides on the homologous portions of the sex chromosomes. If this indeed is so, then, as Berlyne et al. point out, the prevalence of families with each sex affected may be taken as a measure of the frequency of crossing-over of the homologous portions of these chromosomes.

FURALTADONE

THE problem of controlling infection due to *Staphylococcus aureus* resistant to the common antibiotics is by now all too familiar. Nearly three years ago a new nitrofuran—furaltadone—was introduced for the oral and intravenous treatment of bacterial infections; and it was particularly recommended for use against the resistant staphylococcus.

McCarthy and Finland [10] have compared the antibacterial activity of furaltadone in vitro with that of the serum of patients receiving furaltadone (given by intravenous infusion to avoid errors due to defective intestinal absorption) mainly on account of staphylococcal infection, though in some cases this was complicated by infection with gram-negative bacilli resistant to furaltadone.

9 patients who had failed to respond to treatment with various antibiotics were investigated. In two to six days of treatment no patient showed any clinical improvement; and serum from these patients failed to inhibit effectively the organism responsible for the infection, even though in vitro nearly all the infecting organisms were sensitive to furaltadone. A further 12 patients received similar furaltadone infusions (1 g. daily) for four days or more immediately after operation in potentially infected fields. There was no evidence of any antibacterial activity against the susceptible staphylococcus in the serum of any of these patients, 2 of whom developed infections, 1 of which proved fatal.

There are now numerous reports of toxicity. Last year Lee [11] described 4 cases in which, after six or more weeks of treatment with oral furaltadone, there were alarming neurological symptoms and signs, including in 1 case a temporary personality change. Fortunately these disturbances all subsided within a few weeks after the drug was discontinued, and there was no apparent permanent damage.

McCarthy and Finland's report suggests that furaltadone has no therapeutic or prophylactic value. Experience with this drug indicates, not for the first time, that in-vitro activity is no guarantee of effectiveness in vivo.

7. Gillman, T., Penn, J., Bronks, D., Roux, M. *Arch. Path.* 1955, **59**, 733.
8. Loewi, G., Glynn, L. E., Dorling, J. *J. Path. Bact.* 1960, **80**, 1.
9. Berlyne, G. M., Bulmer, M. G., Platt, R. *Quart. J. Med.* 1961, **30**, 201.
10. McCarthy, C. G., Finland, M. *Arch. intern. Med.* 1961, **107**, 863.
11. Lee, M. L. H. *Lancet*, 1960, ii, 374.

CONVERSION OF ST. EBBA'S?

THE need for more beds for mentally subnormal patients is extremely urgent, and in this respect the South West Metropolitan region is the most overcrowded in the country. Its hospitals for the subnormal have about 1200 more patients than they were intended to hold, and there is a waiting-list of some 400. The regional hospital board are very properly concerned at the effect some of these waiting patients are having on their families. Moreover, the number of subnormal patients is rising, with increasing pressure on hospitals from those of the lower grade.[1]

Nevertheless the board's proposal to convert St. Ebba's, Epsom, into a hospital for the mentally subnormal will come as a shock to many. It is the newest psychiatric hospital in the region (half being built early this century, and the other half shortly before the late war) and it is also the smallest, with a capacity of 856 beds, 200–300 of which are occupied by short-stay patients. Because of its considerable physical advantages, it has been used for patients of good prognosis from all parts of the Metropolitan area, instead of being more strictly attached to a catchment area. After the beginning of the National Health Service a notable addition to St. Ebba's was an adolescent unit, run for six years by the medical superintendent, the late Dr. Dalton Sands, and now by a part-time consultant and two junior doctors. More recently the hospital was selected by the Medical Research Council for starting a unit for the study of psychiatric illness. This work is at present being done by Dr. A. J. Coppen and his staff, under the direction of Dr. Derek Richter, and with the conversion of one of the wards (along lines already accepted in principle by the management committee) the unit would have exceptional clinical and scientific research opportunities. Thus St. Ebba's can not unreasonably claim to be the most comprehensive psychiatric hospital in the region, as regards both its range of patients and its psychiatric activities. Hence, it is not surprising that protests are being made at what the local press has described as startling proposals. With these protests come alternative suggestions for finding the needed beds for mentally subnormal patients—perhaps at one of the other mental hospitals within a few miles of St. Ebba's.

Before any conclusion is reached, it should at least be made plain to everybody that all possible alternatives have been fully considered. News of the suggested conversion has come rather suddenly at a time when discussion and communication is hampered by the holiday season; but the board and the hospital management committee have agreed to set up a small working party to examine the plan together, and the board are taking steps to ensure that, before the final submission is made to the Ministry of Health, everyone concerned will have an opportunity to ask questions.

1. Report of the Ministry of Health for the year ended Dec. 31, 1960. Part I: Health and Welfare Services.

Teaching of Everyday Psychiatry *

PSYCHIATRIC EXAMINATIONS AND TEACHING

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ASSESSMENT of the psychiatric teaching of undergraduates is founded on the examination system, and at a time when psychiatric teaching and its effects are the subject of widespread reappraisal and planning the means by which this teaching is tested in the medical school are relevant. Examinations, of whatever kind, should yield information not only about the students who sit them but about the quality and quantity of their instruction. With this in mind our departments have been examining their conventional methods of examination, have introduced experimentally a joint multiple-choice examination, and have assessed the results in terms of the different lengths and emphases of their undergraduate courses in psychiatry.

In the session 1960–61, 10 hours were given to systematic lectures in psychological medicine at Glasgow, compared with 27 hours at Edinburgh. At Glasgow the students are divided into three sections attending a number of hospitals where they are given clinical demonstrations totalling 35 hours, while in Edinburgh 27 hours are devoted to clinical demonstrations and outpatient attendance. In addition, Edinburgh provides an elective course in the preceding year which gives approximately 25 hours of introductory lectures and practical experience in interviewing, and is attended by 85% of the students. In total, Edinburgh provides roughly 80 hours of psychiatric teaching and Glasgow 45. In addition, the examination in Edinburgh ranks as a professional one and contains written, oral, and clinical tests, while in Glasgow there is a written term examination at the end of the course, lasting an hour and not forming part of the professional examinations. In both universities changes are imminent; next session the systematic lectures at Glasgow are to be increased from 10 to 40, and at Edinburgh formal teaching is soon to be radically reduced in favour of instruction in small tutorial groups. If a base-line can be produced, showing in a reproducible way the results obtained with the present courses, then these changes can be more realistically evaluated at a later date. The existing differences in teaching time and academic status of the subject at the two schools are large enough to make comparisons of current results of interest.

MULTIPLE-CHOICE EXAMINATION

The decision to introduce a multiple-choice examination at Glasgow was made partly to provide more information about teaching, partly to test a wider range of information in the short time available, and partly from a belief, well grounded in previous work (see Hubbard and Clemans [1] for a comprehensive bibliography), that multiple-choice examinations are fairer and grade students more reliably than conventional essay questions. Originally 120 multiple-choice questions were constructed. These were screened on small groups of postgraduate students; those that were too easy, too difficult, or ambiguous were rejected; and 70 were chosen for the undergraduate examination. In content they covered psychiatric symptomatology and therapy for the most part, but some questions on related topics were included —e.g., epidemiology, psychoanalysis, clinical psychology, electroencephalography. Questions were not confined to points dealt with in the course and included items that the undergraduate who had read something more of the subject than an introductory text could be expected to answer; for example, a question concerning a number of names well known in psychiatry and related fields:

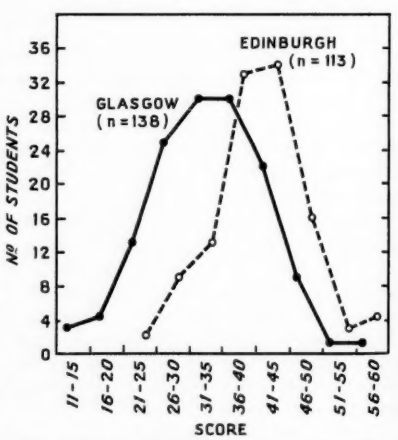
Q. From the names on the left select the one that is closely associated with each subject on the right.

1. Janet	H. Thinking in children
2. Lorenz	I. Homosexuality
3. Bowlby	J. Somatotyping
4. Freud	K. Maternal deprivation
5. Kraepelin	L. Dementia praecox
6. Wolfenden	M. Electroencephalography
7. Piaget	N. Anal-erotic character
8. Sheldon	
9. Berger	

Of the seven names to be identified, at least three would be mentioned in lectures, three are well enough known to have had paperback editions of their books issued in this country, and one should be familiar to any newspaper reader.

At the examination these 70 questions were given, together with an essay question which gave a combination of psychiatric symptoms and asked for a discussion of differential diagnosis, investigation, and possible treatment. Few students had difficulty in completing the paper within the hour. In Edinburgh the same 70 questions were set some weeks after the usual professional examination of three parts had been given and the results made known. Thus in Glasgow the results of the multiple-choice examination could be compared with the results of an essay question answered at the same time, while in Edinburgh they could be set against the scores for the three parts of the conventional examination.

The distribution of scores out of a possible 70 is shown for the two classes in the figure. One mark was given for each correct answer. No marks were subtracted for guessing as scoring a sample of the papers with a correction for guessing made no difference to the rank order. The 113 Edinburgh students had a mean of 40, S.D. = 6·9, the 138 Glasgow students a mean of 34·3, S.D. = 8·25. The better performance of the Edinburgh students is obvious and significant beyond the 0·01 level (C.R. = 6·2). However, the larger range and standard deviation of the Glasgow group suggests that the questions, framed by Glasgow examiners, discriminated rather better between the Glasgow students than between the Edinburgh ones.



* A series of articles on the needs of students and practitioners, and how they may be met.

1. Hubbard, J. P., Clemans, W. V. Multiple-Choice Examinations in Medicine. London, 1961.

Subsequent item analysis traced this difference to specific questions.

Why should the Edinburgh students be so clearly superior on this test? There is no reason to suppose that selection procedures differ greatly at the two universities, and the hurdles of earlier professional examinations must have had an equalising effect on the two groups: hence great differences in intellectual calibre between them can be excluded with some confidence. The difference in time allotted to the specialty must be relevant, and it is possible that time spent on formal lectures as opposed to clinical instruction is rewarded by higher marks on this type of test. But in learning motivation is as important as the amount of time devoted to a task. The student is more strongly motivated to study a subject if he has to pass a professional examination than if he faces only a class test, and this difference between the two classes is likely to be as important as the number of hours devoted to their teaching.

CONVENTIONAL EXAMINATIONS AND MULTIPLE-CHOICE QUESTIONS

The correlation between marks on the essay question and the multiple-choice examination for the 138 Glasgow students was $r = 0{\cdot}47$ ($P > 0{\cdot}01$). In addition, at the end of the Glasgow examination a random sample of 40 essay questions was taken and these questions marked by the four examiners who later shared the marking of all the questions. Each of the four marked all 40 questions without knowledge of the marks given by the other three or of the multiple-choice results of these students. The intercorrelations of these marks are shown in table I.

Examiners A, B, and C correlate significantly with each other and with the multiple-choice results, but examiner D shows less agreement. One of the examiners had long experience of marking undergraduate papers, one had a few years, and two were inexperienced. The differences in experience were not reflected in the correlations obtained; indeed the highest correlation (0·92) was between the two inexperienced markers.

TABLE I—PRODUCT—MOMENT CORRELATIONS BETWEEN FOUR EXAMINERS ON ONE ESSAY QUESTION AND WITH MULTIPLE-CHOICE EXAMINATION

—	Essay question				Multiple choice
	A	B	C	D	
Examiner A ..	..	+0·83*	+0·58*	+0·41*	+0·54*
„ B ..	..	..	+0·92*	+0·12	+0·55*
„ C ..	..	..	..	+0·52*	+0·46*
„ D ..	..	..	..	..	+0·14
Multiple choice	..	..	..	..	..

* = Significant at 1% level.

Some of the correlations were higher than those usually found in this type of test. The fact that the essay question was divided into three parts and the markers instructed to allot a definite number of marks to each probably accounts for this. The correlations are similar to those obtained for final examinations in medicine by Bull [2] who showed that the correlation rose as the length of question fell—an effect achieved here by subdividing the question. As in previous work no difference was found between those marking on total impression and those marking on detailed points made.

The efforts of the markers as a group cannot be considered efficient, for an analysis of variance shows that only 25% of the total variance is attributable to the students, the rest being attributed to the examiners and interaction. As to the multiple-choice examination, results correlate significantly with the conventional methods of assessment and suggest that the two methods are tapping similar information and ability.

2. Bull, G. M. *Lancet*, 1956, ii, 368.

TABLE II—PRODUCT—MOMENT CORRELATIONS BETWEEN FOUR TYPES OF EXAMINATION SET AT EDINBURGH

—	Clinical	Oral	Written	Multiple C
Clinical ..	..	+0·33	+0·26	+0·25
Oral ..	..	..	+0·43	+0·26
Written ..	..	..	..	+0·44

All these correlations are significant beyond the 0·01 level.

In Edinburgh intercorrelations were calculated between the four types of test set—the clinical, oral, and written parts of the professional examination, together with the multiple-choice test (table II).

They are low but all significant. The closest relationships are obtained between the multiple-choice and written papers, and between the written and oral tests. As the oral marks must be affected by the examiner's prior knowledge of the candidates' written results, the correlation of 0·43 between written and oral will reflect this contamination. The equally high correlation between the two completely independent test procedures, the written and multiple-choice, is a much more significant finding. Obviously multiple-choice questions could be introduced into future professional examinations with confidence in their ability to produce comparable results, and with the advantage to the examiners of sampling a wider range of knowledge in a more objective way.

APPLICATION TO TEACHING PROBLEMS

In both schools the results obtained from the multiple-choice examination have been helpful in elucidating teaching problems.

In Glasgow students receive the bulk of their instruction in clinical sections from a number of teachers, and only a third of the year are taught throughout by the staff of the professorial unit. In the past it has been a source of concern to the latter that in setting and marking the examination they might unintentionally favour those they had taught personally, either by setting questions from their own teaching, or by being more receptive to their own views and antagonistic to the views of the extra-professorial teaching staff as expressed by their students.

It was possible to eliminate the first source of difficulty by asking all teachers concerned to contribute their share of the questions, but impossible to allow for the second. It was thought that the objective type of examination would correct much of this bias, and this was proved to be the case, the means of the three sections of the class not differing significantly. Item analysis showed that there were fairly large differences between the groups on a few questions, and these were seen to be due to specific differences in teaching. For example, those who attended a unit with a department of electroencephalography scored highly on questions on psychiatric aspects of epilepsy and the E.E.G., while those who had had some teaching from a psychoanalyst answered more questions correctly on psychodynamics and psychoanalysis.

In a previous study of examinations at Glasgow, Lennox, Anderson, and Moorhouse [3] found that students whose native language was not English were handicapped in the essay question. In the present examinations the 15 students at Glasgow who fell into this category did not differ from the others on the essay question but scored significantly lower on the multiple-choice paper. In Edinburgh 10 such students did not differ from their fellow students on either the essay or the multiple-choice test. As the numbers are small, too much reliance should not be placed on these results; but they do not support the view that the student less well acquainted with English suffers in the marking of essay questions. The examiner marking such a paper is likely to make considerable allow-

3. Lennox, B., Anderson, J. R., Moorhouse, P. *ibid.* 1957, ii, 396.

ances for the language difficulty and in the objective examination, with its frequent negative questions, comprehension could well be as great a stumbling-block as expression is in the essay.

An item analysis was made in both schools of the top and bottom 20%. From this sample "total correct" scores were calculated, in order to identify easy and difficult questions. Questions answered correctly by over 80% of the sample were considered too simple: there were 15 of this kind at Edinburgh and 7 at Glasgow, reflecting the higher scores of the Edinburgh students. All 7 of the questions found easy in Glasgow were found easy in Edinburgh. Questions answered correctly by less than 20% were considered difficult, and of these there were 8 from Edinburgh and 7 from Glasgow, 4 of which were identical.

To find those questions which discriminate well between the successful and unsuccessful students, those showing more than a 20% difference between the top and the bottom group were selected. There were 27 such questions in the Glasgow and only 9 in the Edinburgh sample, further evidence that the examination was superior in discriminating among the Glasgow students. Questions that showed a difference of less than 10% between top and bottom groups—and were therefore poor discriminators—numbered 24 for Edinburgh and 18 for Glasgow. These could be regarded as wasteful questions which yield little useful information about the students. However, the easier questions in this group have a useful "buffer" effect which encourages the student. Nevertheless the high number of poor discriminators is an indication that most of them can be omitted in future and other questions substituted. If the questions had been pretested on an undergraduate population many of them could have been identified, but they are inevitable in the early trials of this type of test and their recognition is the first step in refining the test.

Viewed as a whole, the item-analysis confirms the better performance of the Edinburgh students and the better discrimination among the Glasgow ones, and indicates that despite differences in teaching the classes at the two schools find the same questions easy and the same ones difficult.

An attempt was made to carry this further by analysing the differences according to content, dividing the questions into groups dealing with therapy, symptomatology, mental deficiency, &c. Few striking findings emerged, the similarity between the two classes again being more obvious than any differences. The answers given to the question on names given above will illustrate this. Most of the doctors of tomorrow, whether they study at Glasgow or Edinburgh, recognise Wolfenden as being associated with homosexuality, Kraepelin with dementia præcox, and Freud with anal-erotic character; but Lorenz, Bowlby, Piaget, Sheldon, and Berger are names familiar to only a small minority. Those who do know them do well in the test as a whole.

DISCUSSION

The objective type of examination has many critics, not least in psychiatry, but many of the criticisms advanced are misdirected. For example, the objection may be raised that the questions used do not measure the students' ability to form good psychotherapeutic relationships with their patients: such criticism is more properly directed at all written examinations in psychiatry. Clinical acumen can be judged as accurately or inaccurately in objective questions as in essay questions. Any examination that aims to attach importance to clinical abilities and personal qualities in the student should contain both clinical and oral tests.

Other critics believe that education should be independent of any kind of examination and deplore attempts to use them as the main assessments or incentives. An editorial in this journal [4] rejected the view that examinations are the only effective way to make the average student take a subject seriously and considered that "there can be but poor training while such views dictate policy". Our findings suggest that results are better where the student has the professional examination as an incentive. It is unlikely that examinations will be totally superseded in the foreseeable future and it is obscurantist not to make what use of them we can to appraise whatever changes in the curriculum are introduced in response to fashion or logic.

Our preliminary experience with a multiple-choice examination suggests that this technique is a valuable addition to conventional examination procedures. The following advantages are apparent:

1. *The breadth of the topics covered.*—The student can be examined in every area in which he has received instruction or is expected to be informed.

2. *Teaching emphasis.*—Topics can be introduced into the examination in numbers which best reflect the teaching emphasis of the school.

3. *Evaluation of teaching.*—Content-analysis allows the teacher to assess the effectiveness of his instruction in different areas of the curriculum and of the several teaching techniques which he may have employed.

4. *Objective standards.*—The multiple-choice examination introduces standards which are less contaminated by examiner-error. In addition, this objectivity permits comparison of results between schools as well as comparison of teaching techniques within a school.

This last point is of particular interest to us. In one of the universities under consideration formal lectures are to be drastically curtailed, in the other as drastically expanded. The policies are at variance, yet both have good arguments to support them. With the facts now available the policies can be assessed by the changes they produce in the results of annual examinations, and if a policy of joint examinations is pursued by the two universities the measurement of differences between the two will furnish increasingly reliable and valuable information.

We are indebted to Prof. G. M. Carstairs and Prof. T. Ferguson Rodger for permission to carry out this work and to publish the examination results, and for their advice and encouragement.

4. *Lancet*, 1956, ii, 385.

Special Articles

RECENT ADVANCES IN PHRENOLOGY

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THERE is little virtue in inventing new names when old ones are adequate. "Neuropsychology" has recently been coined on the other side of the Atlantic,[1] but "phrenology" is more than a century and a half old. Dr. Cranium [2] has long been a subject of ridicule, but much phrenological theory is in fact acceptable today. Few would oppose the assertion that the brain is the organ of the mind, and most of us would accept the contention that the functions of the mind can be analysed into a number of "faculties", though we would perhaps be a little more empirical about defining these functions. There would be some dissension about the localisation of faculties in definite regions of the cortical surface, but the claim that the relative amount of a faculty is proportional to the area of the region subserving it is implicit, for lower functions at any rate, in the sensory

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1. Hebb, D. O. The Organization of Behaviour. New York, 1949.
2. Peacock, T. L. Headlong Hall. London, 1816.

and motor homunculi so ingeniously represented by Penfield.[3] The attempt to relate the contour of the skull to the size of these cortical regions, and dubious therapeutic manœuvres based on this hypothesis, would not be supported; but lack of support for the phlogiston theory did not bring physics to an end, nor necessitate its being renamed.

The widest disagreements are on the localisation of intellectual functions; and the grounds for disagreement have been confused by uncertainty as to how (if at all) to subdivide the intellect. For neurologists, the argument crystallised round the phenomenon of aphasia:

Here undoubtedly was a deficit of a psychological kind associated with a localised lesion; but was there also impairment of intelligence? More psychological deficits came to be included as localising signs in clinical neurology: disturbances of calculation and construction were associated with lesions of the left parietal lobe; disturbances of spatial perception with right parietal lesions; personality changes with frontal and temporal lesions (with the suggestion that these were commoner with right than with left hemisphere lesions [4 5]); but opinion remained divided on the question of selective intellectual deficit. At the extreme " unitary " end of the scale, Goldstein [6] and his school have stated that " to speak of the condition of intelligence in aphasic patients in general and its maintenance or deficit is impossible ": disturbances in speech, and in non-language performances, " are simply the effect of the same dedifferentiation of brain function in two performance fields ". At the " atomistic " extreme is the viewpoint of Henschen,[7] who held that " centres with sharp localisation are the workshops of the mind ". An intermediate position is that of Hughlings Jackson,[8] who regarded intellectual functions as of two kinds or " series ". After observing the different effects of left and of right hemisphere lesions, he concluded that a left-sided lesion disturbed " propositional " aspects of the language series, while a right-sided lesion impaired non-verbal functions at a similar level. Yet another point of view is that of Marie,[9] who held that " in every aphasic there is a general intellectual deficit, and a specific language-intelligence deficit ", thus anticipating the division of intelligence into general and special abilities. Only memory loss—i.e., impairment of registration of new material, involving memory for recent events—is generally accepted as the commonest psychological sign of cerebral disease, whether the pathological process is localised in the cortex or subcortex, or is diffusely spread.

THE STRUCTURE OF INTELLIGENCE

Without any measure of intelligence, and therefore without the means of establishing an association between lesions in different parts of the cerebrum and impairment of different aspects of intelligence, elaboration of these viewpoints were little more than scholastic exercises. By the turn of the century, however, a number of tests of intelligence had been devised, and an empirical approach became possible. The earlier studies lent support to the " unitary " point of view:

Binet's intelligence test,[10] though comprising a great variety of problems, yielded a single measure which was later standardised as the intelligence quotient, with the consequence that intelligence is widely thought of as a single attribute. Spearman [11] examined the intercorrelations of scores of normal people on a number of different tests, and showed that these could be explained by the assumption of a single factor of general intelligence (called *g*), and specific factors related to the material of each test. Memory tests, however, did not correlate highly with *g* tests, and Spearman held that " retentivity " was a factor not closely related to general intelligence. Further support came from the animal experiments of Lashley,[12] who showed that the degree of impairment of maze-learning ability in the rat depended not on the locus but on the amount of removal of cerebral tissue.

Since these studies were published, opinion on the cerebral representation of intelligence has generally leaned toward the unitary point of view; but in fact no sooner had the edifice been set up than it was being undermined:

Lashley himself was aware that his identification of learning capacity with intelligence might not be justified, and that his studies, being " measures of mnemonic capacity ", might be " irrelevant to the problem of intelligence ". As further evidence accumulated, particularly from human studies, Lashley's point of view changed from " total equipotentiality " to " areal equipotentiality ", though still with the insistence that the degree of disability—e.g., in aphasia—was proportional to the amount of " language area " destroyed.[13] At the same time, the analysis of normal intelligence was greatly enlarged, and many workers showed that test results could validly be ascribed to the operation of a number of *group* factors, rather than to a single *general* factor, as proposed by Spearman.

Different mathematical techniques resulted in identification of slightly different groups, but a general picture emerged of four clear groups—verbal, spatial, numerical, and memory—with the possibility of a number of subsidiary groups, such as reasoning,[14] and constructional ability.[15] The evidence for the major group factors was eventually accepted by Spearman [16]: except for memory, these group factors show fairly high intercorrelations, suggesting that intelligence has an hierarchical structure, with an overall general factor, group factors, and specific abilities related to each test.

Moreover, much evidence related the psychological findings to neurological material:

The most impressive was Weisenburg and McBride's study [17] with standardised tests of a series of aphasic patients, together with a group with comparable right-hemisphere lesions. Comparison of these results with those of normal subjects led Weisenburg et al.[18] to state that " the evidence for a distinction between different groups of mental abilities (in normals) gains additional support from the findings for the pathological groups studied by the same tests. Cases of right-sided cerebral lesion without aphasia . . . were found to be significantly inferior to the normal only on the arithmetic and some of the non-language tests ", while " only a few aphasic patients have anything like as great difficulty in non-language as in language work ". They concluded that " there are in all probability more or less independent groups of mental abilities. The typical normal adult does not show great differences in the development of these abilities . . . In cases of brain disease, however, or at least in cases of localised brain disease, they may be affected unequally ".

Another important study was that of Rylander [19] on the effects of frontal-lobe lesions. On a wide range of psychological tests, he demonstrated the frequency of personality change, of defects of insight and attention, and of difficulty on a test of arranging pictures to tell a story in the absence of impairment of language, perception, or execution.

A glance back at the list of mental abilities identified by factor analysis (verbal, numerical, spatial, constructional,

3. Penfield, W., Boldrey, E. *Brain*, 1937, **60**, 389.
4. Gianelli, P. *Policlinico*, 1897, **4**, 301.
5. Golla, F. L. *Proc. R. Soc. Med.* 1931, **24**, 997.
6. Goldstein, K. Language and Language Disturbances; p. 119. New York, 1948.
7. Henschen, S. E. *Arch. Neurol. Psychiat., Chicago*, 1925, **12**, 226.
8. Jackson, J. H. (1874) *in* Selected Writings of John Hughlings Jackson (edited by J. Taylor, G. Holmes, and F. M. R. Walshe); vol. II. London, 1932.
9. Marie, P., cited by Moutier *in* L'Aphasie de Broca. Paris, 1908.
10. Binet, A. *Année psychol.* 1911, **17**, 150.
11. Spearman, C. The Abilities of Man. London, 1932.
12. Lashley, K. S. Brain Mechanisms and Intelligence. Chicago, 1929.
13. Lashley, K. S. *Trans. Amer. neurol. Ass.* 1949, p. 147.
14. Thurstone, L. L., Thurstone, T. G. *Psychometr. Monogr.* 1941, no. 2.
15. Alexander, W. P. Intelligence, Concrete and Abstract. Cambridge, 1935.
16. Spearman, C., Wynne Jones, L. L. Human Abilities. London, 1950.
17. Weisenburg, T. H., McBride, K. E. Aphasia. New York, 1935.
18. Weisenburg, T. H., Roe, A., McBride, K. E. Adult Intelligence. New York, 1936.
19. Rylander, G. *Acta psychiat., Kbh.* 1939, suppl. 20.

mnemonic) shows the identity of the processes involved to those impaired in the clinical conditions (aphasia, acalculia, spatial agnosia, constructional apraxia, recent memory) with the added similarity that memory occupies in both cases a somewhat exceptional position. One might reasonably expect that impairment of individual abilities would be found with lesions localised in those areas associated with the corresponding clinical deficits. With the publication of Wechsler's intelligence scales,[20 21] confirmation of this view became a practical possibility, and many workers have discussed the results of testing neurological patients. Not only do Wechsler's scales comprise a number of subtests covering a wide range of intellectual functions—e.g., arithmetic, verbal intelligence, constructional ability, pictorial analysis—but the scores are so adjusted as to make them comparable between subtests for each individual, thus enabling the tester to identify particular constellations of ability or disability.

Considering major subdivisions of the cerebrum, two broad distinctions have been made: precentral lesions generally result in less test impairment than do postcentral ones [22 23]; and verbal tests are impaired more with left-hemisphere lesions, and non-verbal tests with right-hemisphere lesions.[24 26] More precise associations between location of lesion and type of deficit have also been demonstrated in a number of studies:

Milner [27] reported impairment on the picture-arrangement subtest with temporal-lobe lesions, and on verbal subtests with left temporal lesions; more recently [28] she has reported specific deficits on another pictorial test (McGill picture anomalies) associated with *right* temporal lesions. McFie and Piercy [29] reported 58 cases with localised cerebral lesions, and found the

GROUPING OF INTELLECTUAL IMPAIRMENT ACCORDING TO SITE OF LESION (from McFie [31])

Site of lesion	Tests showing greatest impairment
Left frontal	Digit span, sentence learning
Left temporal	Digit span, sentence learning, similarities
Left parietal	Digit span, sentence learning, arithmetic, block designs, Weigl's sorting
Right frontal	Picture arrangement, memory for designs
Right temporal	Picture arrangement, memory for designs
Right parietal	Picture arrangement, memory for designs, block designs

expected association of impairment on verbal subtests with left-hemisphere lesions, on calculation and construction subtests with parietal lesions, and on the picture-arrangement test with right frontal and right temporal lesions. Similar results associating lesions of the parietal and temporal lobes with verbal, constructional, and pictorial subtests of the Wechsler scale were reported by Reitan [30]; while a recent survey by McFie [31] of over 200 patients has confirmed the pattern of deficits associated with lesions in each of the major cerebral lobes.

The table shows the Wechsler subtests, and other tests, on which the lowest average scores were found in each group. Considering the subject matter of each test it is evident that verbal memory span and verbal learning are impaired in all groups with left-hemisphere lesions; with left temporal lesions verbal intelligence (as tested by similarities) is profoundly affected; and with parietal lesions arithmetic, abstraction (Weigl's test), construction, and pictorial arrangement are also impaired. With right-hemisphere lesions the common deficit is in memory for visual (drawn) material, and also in picture arrangement; with temporal lesions the latter deficit is greatest; and with parietal lesions there is also profound impairment on the constructional test. Because there are more patients than in earlier studies, this survey gives additional support to the hypothesis of selective impairment of intellectual functions, and indicates clearly the association between site of damage and specific deficit.

SUBCORTICAL LESIONS

The most constant relation between location of lesion and type of intellectual deficit is found in cases of tumour and other injury involving the cortical surface. However, it seems likely that similar relations exist in cases of persistent focal electrical disturbance (which may, of course, be no more than an early manifestation of a lesion), as suggested in recent reviews.[32 33] Lesions in the thalamus or the globus pallidus, made for relief of parkinsonian symptoms, also produce different patterns of impairment according to the side operated upon. Riklan et al.[34] and McFie [35] both found, as might be expected, losses on verbal tests in those operated on the left, and in performance tests in those operated on the right; but there was little difference between those in which the lesion was in the thalamus or in the globus pallidus.

Studies with adult patients tend to emphasise the constancy of these patterns of impairment; but with children they are less constant, and in cases of birth injury the "conventional" relationships are not found:

Krynauw [36] showed that in cases of birth injury to the left hemisphere, removal (hemispherectomy) did not impair speech. Subsequent studies by Cairns and Davidson,[37] Uecker et al.,[38] and Gardner et al.[39] make it clear that removal of a hemisphere damaged at birth or in the first year does not generally cause intellectual impairment, regardless of the side of removal.

It seems that damage to one hemisphere, before the normal distribution of functions into left and right hemispheres, results in all intellectual functions being mediated by the intact hemisphere.

CLINICAL APPLICATION

In the more advanced cases of impairment, the association of intellectual deficit with the corresponding clinical condition (e.g., verbal deficit with dysphasia) is made obvious by their coexistence: but among the patients whose test scores are represented in the table, not more than 25% showed evidence of psychological deficit on clinical examination.

Evidently impairment of intellectual abilities may be detected before the neurological condition becomes manifest: and herein lies a great part of the clinical usefulness of these tests. In this context, a patient's test results are considered not to see which scores differ significantly from the population average but to see whether the pattern of deficits corresponds to the syndrome associated with a particular lesion, as Piercy [40] has suggested. In this series [30] 75% of the patients' results showed greatest impairment in the tests indicated in the table, or, in other words, the site of the lesion would have been correctly predicted in 75%. The impairment of the remaining 25% of the patients showed various deviations from the "expected" pattern, as would be anticipated from the relatively crude measures in-

20. Wechsler, D. The Measurement of Adult Intelligence. New York, 1944.
21. Wechsler, D. The Measurement and Appraisal of Adult Intelligence. New York, 1958.
22. Morrow, R. S., Mark, J. C. *J. cons. Psychol.* 1955, **19**, 283.
23. Chapman, L. F., Wolff, H. G. *A.M.A. Arch. Neurol.* 1959, **1**, 357.
24. Anderson, A. L. *J. clin. Psychol.* 1951, **7**, 149.
25. Reitan, R. M. *J. comp. physiol. Psychol.* 1955, **48**, 474.
26. Heilbrun, A. B. *ibid.* 1956, **49**, 10.
27. Milner, B. *Psychol. Bull.* 1954, **51**, 46.
28. Milner, B. *Proc. Ass. Res. nerv. Dis.* 1958, **34**, 244.
29. McFie, J., Piercy, M. F. *Brain*, 1952, **75**, 292.
30. Reitan, R. M. The Effects of Brain Lesions on Adaptive Abilities in Human Beings. Indianapolis, 1959.
31. McFie, J. *J. nerv. ment. Dis.* 1960, **131**, 383.
32. Quadfasel, A., Pruyser, P. W. *Epilepsia*, 1955, **4**, 80.
33. Ellingson, R. J. *Psychol. Bull.* 1956, **53**, 1.
34. Riklan, M., Diller, L., Weiner, H., Cooper, I. S. *Arch. gen. Psychiat.* 1960, **2**, 22.
35. McFie, J. *J. ment. Sci.* 1960, **106**, 1512.
36. Krynauw, R. A. *J. Neurol. Psychiat.* 1950, **13**, 243.
37. Cairns, H., Davidson, M. A. *Lancet*, 1951, ii, 411.
38. Uecker, A. E., French, L. A., Johnson, D. R. *Arch. Neurol. Psychiat., Chicago*, 1954, **72**, 555.
39. Gardner, W. J., Karnosh, L. J., McClure, G. C., Gardner, A. K. *Brain*, 1955, **78**, 487.
40. Piercy, M. F. *J. ment. Sci.* 1959, **105**, 489.

volved; but one group was identified whose results would have been expected with lesions of the opposite hemisphere—yet none of these was left-handed. Indeed, the patterns of impairment of the left-handed patients were, on the whole, the same as those of right-handed ones—a finding which lends support to the contention of Penfield and Roberts,[41] based on experience with cortical excisions, that " the left hemisphere is usually dominant for speech regardless of the handedness of the individual ". As a corollary, the right hemisphere is usually " dominant " for certain non-verbal functions.

Another clinical implication of the demonstration that different deficits are associated with lesions in different parts of the cerebrum is that it is illogical to expect that any one test or ratio between scores will provide an indication of " brain damage ": even a group of tests of the kind discussed above would show much less overall impairment with, say, a right frontal than with a left parietal lesion. That certain tests show impairment with cerebral lesions while others do not supports Wechsler's suggestion [20] (based on differential decline of scores with increasing age) that discrepancies between scores on the two types of test may provide an estimate of the effect of a generalised pathological process. In the survey referred to above, a highly significant correlation was found between Wechsler's " deterioration loss " and a radiological estimate of cerebral atrophy in 52 patients, supporting the conclusions of earlier studies.[42–44]

If I have given an impression of unanimity concerning the intellectual effects of cerebral lesions, it has been the result of careful selection of references, for there have been many exceptions to this point of view. Supporters of the Goldsteinian viewpoint (as in the compendious review of Klebanoff et al.[45]) tend to overlook the body of evidence for specific effects of focal lesions. Mathematically minded psychologists (Yates,[46] Jones,[47] Meyer [48]) have criticised clinical studies as uncontrolled, and test results as too unreliable for inference to be drawn. Others (e.g., Critchley [49]) have felt that human behaviour is too subtly variable for such a crude analysis as is implied by allocation of scores. But the ultimate test is the clinical validity of a given method, and for this there is a considerable body of confirmation. This is not to say that there is no room for improvement; and above all it is not to claim that any pattern of test results is itself diagnostic of organic disease, or of a localised lesion. Congenital disabilities, biochemical disorders, and psychiatric states may also be associated with similar patterns of impairment: it is for the clinician to make the diagnosis.

UNSOLVED PROBLEMS

While the demonstration of specific effects of localised cerebral lesions may have given some definition to a rather obscure picture and have brought together points of similarity in neurology and psychology, it has raised a number of problems for the future to solve. Following identification of a " focal " intellectual deficit, the object of analysis is to determine the fundamental psychological disturbance underlying it—in the hope, ultimately, of understanding its neurophysiological basis. For example, impairment on the block-designs test with parietal lesions may be due to a disturbance of normal spatial perception in cases with right-sided lesions,[50 51] but to disturbance of constructional ability in cases with left-sided lesions.[52 53] Lenz [54] and Hécaen et al.[55] have shown neurological disorders of spatial orientation in cases with right parietal lesions; but the nature of the fundamental deficits underlying constructional apraxia, and other psychological disabilities, has not been elucidated.

Not until the fundamental processes underlying intellectual functions have been demonstrated can any assessment be made of the extent of cortex subserving them. In the left hemisphere, for example, relatively few intellectual functions seem to be spread over a relatively large area in the frontal lobe, while a number of functions are crowded into a small space in the parietal lobe. The same fundamental disturbance may possibly be found to underly the various abilities—arithmetical, verbal, constructional, conceptual—impaired in the latter case. An essential requirement for this analysis is careful standardised investigation of groups of patients with lesions as precisely localised as possible: the description of disabilities in cases of widespread cerebrovascular or degenerative disease has little analytical value. Parallels between brains and electronic computers being currently fashionable, the analogy may be drawn between these cases and computers disordered by random bursts of machine-gun fire: no matter how detailed the analysis of the erroneous computations, it will not help us to understand how the computer worked.

An urgent need, too, is for an English group of tests. Beyond the first three years of life (when Griffiths' scale [56] is appropriate) none of the intelligence tests in current use (principally the Wechsler scales) has been standardised on an English population. It is a tribute to the construction of the scales, and to the constancy of human cerebral organisation, that such agreement should be found in experience on both sides of the Atlantic. But without doubt reliance on American standardisation considerably reduces both the clinical and theoretical value of our test results, particularly as cultural differences are more likely to affect some subtest scores than others (Robertson and Batcheldor [57]), thus altering the differences between these scores. There is a need, therefore, for an English standardisation of test scales of the Wechsler type; and there is room, at the same time, for improvement in the constituent subtests of the scale, so that intellectual functions may be more precisely identified. With an improved instrument, and a better understanding of its capabilities and limitations, the road will lie open to considerable advances in understanding of the organisation of the brain.

The intellectual abilities identified by contemporary studies are perhaps a little less picturesque than the faculties proposed by the earlier phrenologists, and physiological inaccessibility may preclude the dramatic treatments which they suggested; but we should at least acknowledge the success of their intuition, and their status as pioneers in the localisation of intellectual functions.

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41. Penfield, W., Roberts, L. Speech and Brain Mechanisms. Princeton, 1959.
42. Levi, J., Oppenheim, S., Wechsler, D. *J. abnorm. (soc.) Psychol.* 1945, **40**, 405.
43. Aita, J. J., Armitage, S. G., Reitain, R. M., Rabinowitz, A. *J. gen. Psychol.* 1947, **37**, 25.
44. Blake, R. R., McCarthy, B. S. *J. clin. Psychol.* 1948, **4**, 415.
45. Klebanoff, S. G., Singer, J. L., Wilensky, H. *Psychol. Bull.* 1954, **51**, 1.
46. Yates, A. J. *ibid.* 1954, p. 359.
47. Jones, H. G. *J. cons. Psychol.* 1956, **20**, 319.
48. Meyer, V. *J. ment. Sci.* 1957, **103**, 80.
49. Critchley, M. The Parietal Lobes; p. 395. London, 1953.
50. McFie, J., Piercy, M. F., Zangwill, O. L. *Brain*, 1950, **73**, 167.
51. Heilbrun, A. B. *A.M.A. Arch. Neurol.* 1959, **1**, 282.
52. McFie, J., Zangwill, O. L. *Brain*, 1960, **83**, 243.
53. Piercy, M. F., Hécaen, H., de Ajuriaguerra, J. *ibid.* p. 225.
54. Lenz, H. *Dtsch. Z. Nervenheilk.* 1944, **157**, 22.
55. Hécaen, H., de Ajuriaguerra, J., Massonet, J. *Encéphale*, 1951, **40**, 122.
56. Griffiths, R. The Abilities of Babies. London, 1954.
57. Robertson, J. P. S., Batcheldor, K. J. *J. ment. Sci.* 1956, **102**, 612.

Public Health

PARATYPHOID FEVER TRACED TO DESICCATED COCONUT

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IN recent years there has been a significant increase in the number of reported cases of food-poisoning, especially due to salmonellæ. Many have been sporadic cases or confined to individual families; and one of the difficulties has been the identification of the vehicle of infection.

During the past two years desiccated coconut imported from Ceylon has revealed on bacteriological examination various salmonellæ, including *Salmonella paratyphi-B*. In 1960, Liverpool Port Health Authority submitted 8265 samples of desiccated coconut to the Public Health Laboratory Service; of these, 479 (5·8%) were infected with salmonellæ, and 42 of the positive samples (8·8%) yielded *S. paratyphi-B*.

Kovacs (1959) isolated salmonellæ, including one strain of *S. paratyphi-B*, from 9 out of 35 samples; and Galbraith et al. (1960) found, between July, 1959, and March, 1960, that 76 (9%) of 851 samples were contaminated with salmonellæ, and in 15 (1·8%) *S. paratyphi-B* was isolated.

Anderson (1960), reviewing the phage-typing of *S. paratyphi-B* in samples of desiccated coconut submitted to the Central Enteric Reference Laboratory between December, 1959, and May, 1960, examined 37 cultures and identified 7 different types (totals in parentheses): *Beccles* (8); *1* var. *9* (6); *Dundee* (3); *Jersey* (1); *Taunton* (1); and untypable (15). With the exception of type *1* var. *9*, all are found in human infection in this country.

Desiccated coconut is widely used in the bakery trade, especially in biscuits, cakes, and pastries, and to decorate cakes, custards, trifles, and jellies. It is also an ingredient of confectionery; and small quantities are bought by housewives. 6288 tons of this foodstuff (of an estimated value of £641,376) were landed at the port of Liverpool in 1960.

On November 21, 1960, *S. paratyphi-B* type *Beccles* var. *4* was identified in a marshmallow biscuit purchased at a Liverpool restaurant. This phage-type was first recognised by Anderson and his coworkers (1961) and they will describe it elsewhere.

The infected biscuit had been manufactured in a Liverpool factory some ten days previously. The coconut in the biscuit had been imported from Ceylon through the port of Liverpool and subjected to a 5% sampling by the port health authority before its release.

BISCUIT MANUFACTURE

A marshmallow biscuit is a flat biscuit, mallow-topped, covered with dried coconut. Each part is prepared separately.

Biscuit.—A standard recipe is used. The biscuit is baked for nine minutes in a travelling oven in which the temperature is raised to 350°F for the final six minutes. The biscuits are packed by hand into trays and stored for up to a week at 80°F and 30% relative humidity until they are required.

Mallow.—Made to a standard formula, the mix is warmed to 170°F, and cooled to 140°F. Water with dissolved gelatine is added. The mixture is then cooled to 95°F over a $1^1/_2$-hour period. The total time for mixing is approximately 8 hours. Finally the mallow is aerated to a bulk density of about 0·26 before being deposited on the biscuit.

Coconut.—The coconut is stored in 100-lb. multi-wall paper bags at a temperature of 45–50°F. It is put through a mill which breaks up the lumps and stored in a steel drum at the same temperature (45–50°F) until required by the mallow department.

After the mallow is deposited on the biscuit, coconut is sprinkled on the top through a vibratory sieve, while the whole biscuit is moved forwards on a conveyor belt. It passes into a chamber at 117°F for 25 minutes, then into a second chamber, heated to 65–70°F and at 50% relative humidity, for a further 25 minutes. The finished product is packed by hand, either into tins or 'Cellophane' packets, which are automatically sealed.

All twenty-four girls employed in packing the biscuits were examined. Only one gave a recent history of enteritis, and she was bacteriologically negative on repeated examination.

An experiment was next conducted to establish whether an ingredient of the marshmallow biscuit was the source of infection.

EXPERIMENTS

Experiment I.—Samples of marshmallow biscuit (a packet of 12 to a sample) and desiccated coconut (125 g. to a sample) used in making the biscuits were taken at the factory over a period of seven days. In all, 59 samples of coconut and 59 finished biscuits were examined bacteriologically. The findings were as follows:

Desiccated coconut		*Marshmallow biscuit*	
S. paratyphi-B—Dundee var. *2* ..	1	*S. meleagridis*	13
S. paratyphi-B—Beccles var. *4* ..	3	*S. hvittingfoss*	1
S. paratyphi-B—Battersea	1		14
S. hvittingfoss	7		
S. waycross	1		
S. bareilly	1		
	14		

These results indicate that salmonellæ can be irregularly scattered in the coconut, and the temperature reached in the preparation of the finished biscuit is insufficient to destroy the salmonellæ present.

Experiment II.—12 samples of dried whole egg, of frozen whole egg, and of frozen egg white sometimes used to prepare mallow were next examined. All were negative.

5 samples of gelatin used in mallow manufacture were positive for *S. meleagridis*. This suggests that gelatin should be further investigated.

CLINICAL CASES OF PARATYPHOID FEVER

Case 1.—In December, 1960, paratyphoid fever developed in a young boy in Redditch; *S. paratyphi-B* phage-type *Beccles* var. *4* was the infecting organism. In the same household 2 symptomless excretors of the same phage-type were found. The vehicle of infection was marshmallow biscuit; the contents of an unfinished packet found in the house were shown to be infected (Drawneek 1961).

These biscuits came from the Liverpool factory mentioned above, and 12 of them, the rest of the consignment, were recovered from the shop in Redditch which supplied biscuits to the boy with paratyphoid. Each biscuit was divided into four; and *S. paratyphi-B* phage-type *Beccles* var. *4* was isolated from all 12. Of 17 further samples of the biscuit collected from many parts of England 1 contained *S. meleagridis* and 1 *S. thompson*.

Case 2.—In March, 1961, a 5-year-old child with enteritis was admitted to a hospital in Coventry; *S. paratyphi-B* type *Beccles* var. *4* was isolated from two specimens of her stools. She had eaten marshmallow biscuits bought in a Coventry store; they had been made in the same Liverpool factory (Clayton 1961).

Case 3.—In Liverpool, later in the same month, a baby of 10 months had paratyphoid fever; the organism was indentified as *S. paratyphi-B* type *Beccles* var. *4*. The parents had given the baby bits of coconut-covered biscuit some 10–15 days before

the illness began. Two older children in the same household, aged 6 and 4, were found to be symptomless excretors of this same phage-type; these children had also eaten the biscuits. There were no biscuits left in the house, but samples from the shop where they were bought were examined. *S. paratyphi-B* was not found in any of them; but in one sample *S. ferlac* was identified. This phage-type had already been isolated from imported desiccated coconut sampled at the Port.

The biscuit manufacturing company recalled all these marshmallow biscuits from the retailers; and desiccated coconut is no longer used as a top dressing for its biscuits.

DISCUSSION

Transmission of enteric fever by desiccated coconut was first observed in Australia in 1953, when an outbreak of typhoid fever due to *S. typhi* Vi-phage *E.1* was traced to coconut from Papua (Wilson and Mackenzie 1955). In 1960, paratyphoid fever in a Lancashire maternity hospital involved 9 adults and 5 infants (2 cases and 12 symptomless carriers) (Anderson 1960). All were infected with *S. paratyphi-B* phage-type *1* var. *9*. The first patient, a pregnant woman, had eaten large quantities of raw desiccated coconut and had had gastroenteritis for four weeks before being admitted to the maternity hospital, where it is thought that she communicated the disease to the others.

In this outbreak a new phage-type of *S. paratyphi-B* was discovered: this, a subtype of type *1*, was designated *1* var. *9* and was first isolated at the Food Hygiene Laboratory, Colindale, from desiccated coconut from a consignment in the Port of London. Within a few days similar organisms were isolated from coconut from Liverpool as well. In addition, in May, 1960, a number of apparently sporadic cases due to this new type were reported from different parts of the country; most of the patients had eaten cake containing desiccated coconut.

S. paratyphi-B phage-type *Beccles* var. *4* in Liverpool survived for several weeks on coconut-covered marshmallow biscuits, sealed in cellophane, until they were eaten by the boy at Redditch. We conclude from our experiments that salmonellæ survive the baking process in the manufacture of a marshmallow biscuit, both in the mallow itself (*S. meleagridis* in the gelatin) and in the coconut sprinkled on the finished product (*S. hvittingfoss*). That *S. paratyphi-B* was not isolated from the finished biscuit, as it was from the desiccated coconut before baking, was probably only because so few samples were taken. Apparently, organisms in dried coconut can survive the low-temperature baking of marshmallow biscuits (viz., 117°F for 25 minutes, followed by 65–70°F for 25 minutes). The margin of safety with toasting procedures is a narrow one: *S. thompson* survived 12 minutes but not 12½ of " toasting " at 400°F, in a ' Reel ' oven, and 15 minutes but not 17 at 400°F in a ' Peel ' oven (Seiler 1960.) In preparing the marshmallow biscuits in Liverpool, only sufficient heat was applied to ensure that the mallow would be hard enought not to run over the biscuit. Toasting was avoided to preserve the appearance of the coconut.

Our findings indicate that contaminated coconut was released to the bakery trade; the sampling procedures for coconut are clearly not effective.

In an experiment in Liverpool (Semple et al. 1961), a 100-lb. bag of desiccated coconut withdrawn because of contamination by *S. paratyphi-B* was sampled, several samples being taken daily. Samples after the fiftieth were all negative. Thus, infection is not necessarily homogeneous throughout a bag; a single sample or even several samples cannot be accepted as representative. Undoubtedly many bags are released in which contamination would be revealed by more thorough sampling.

Desiccated coconut will be safe only if it is prepared in its country of origin in such a way as to be bacteria-free. Failing this, all imported coconut must be sterilised on arrival.

Bakers should be informed of the dangers of desiccated coconut; that it may cause cross-infection, and that handling or packing it may be a health hazard.

SUMMARY

In 3 confirmed cases of paratyphoid fever, *Salmonella paratyphi-B* type *Beccles* var. *4* was identified. Infection was traced to desiccated coconut, which was an ingredient of marshmallow biscuits.

The present measures for ensuring that imported desiccated coconut is safe for human consumption are inadequate.

We are grateful to Prof. D. T. Robinson and to Dr. E. C. Armstrong of the Liverpool Public Health Laboratory Service for the bacteriological examinations.

REFERENCES

Anderson, E. S. (1961) Personal communication.
— (1960) *Mon. Bull. Min. Hlth Lab. Serv.* **19**, 172.
Clayton, T. M. (1961) Personal communication.
Drawneek, W. (1961) Personal communication.
Galbraith, N. S., Hobbs, B. C., Smith, M. E., Tomlinson, A. J. H. (1960) *Mon. Bull. Min. Hlth Lab. Serv.* **19**, 99.
Kovacs, N. (1959) *Med. J. Aust.* **i**, 557.
Seiler, D. A. L. (1960) *Mon. Bull. Min. Hlth Lab. Serv.* **19**, 211.
Semple, A. B., Graham, A. J., Dutton, E. M. (1961) *Med. Offr*, **105**, 59.
Wilson. M. M., Mackenzie, E. F. (1955) *J. appl. Bact.* **18**, 510.

Safety Code for Ionising Radiations

A safety code for workers exposed to ionising radiations in industry is laid down in the Ionising Radiations (Sealed Sources) Regulations, 1961,[1] presented to Parliament last week. Most of the requirements will come into operation in six months, but those requiring the notification of the use and disuse of ionising radiations in factories will be effective from Aug. 15.

The regulations require the restriction of the exposure of workers to radiation, the adequate shielding of sources of ionising radiations, and the instruction of workers likely to be exposed about the hazards involved and the precautions to be taken. Maximum permissible doses of radiation are laid down, and the regulations include requirements for the medical supervision of workers and the wearing of film badges.

1. S.I. no. 1470. H.M. Stationery Office. 9*d*.

Infectious Diseases in England and Wales

Diseases	Week ended July				
	1	8	15	22	29*
Diphtheria	..	5	5	3	3
Dysentery	432	467	403	345	470
Encephalitis:					
Infectious	4	2	7	1	3
Postinfectious	4	6	3	3	2
Food-poisoning	191	213	278	191	206
Measles, excluding rubella	15,248	13,222	12,435	10,397	9,958
Meningococcal infection	28	29	20	13	15
Ophthalmia neonatorum	13	23	17	15	20
Paratyphoid fever	3	3	4	3	7
Pneumonia, primary or influenzal	203	158	162	118	139
Poliomyelitis:					
Paralytic	12	20	8	11	22
Non-paralytic	3	5	2	8	5
Puerperal pyrexia	163	123	139	165	157
Scarlet fever	358	310	295	308	346
Smallpox	..	..	..	..	..
Tuberculosis:					
Respiratory	407	362	386	372	383
Meninges and C.N.S.	4	5	7	4	3
Other	54	55	53	69	49
Typhoid fever	..	3	5	1	..
Whooping-cough	499	408	416	397	414

*Not including late returns.

Strontium 90 in Human Bone

In the second [1] of the Medical Research Council Monitoring Report Series, containing results of measurements of strontium 90 in human bone in the United Kingdom, a new section is included giving the results of some analyses of material from stillborn fœtuses. Comparison of the results from the two main centres (Woolwich and Glasgow) with those for 1959 show that in children between 0 and 5 years there has been relatively little change in the average values of strontium 90 in bone. The average level in this group for the first half of 1960 was 3·3 strontium units, compared with 3·2 S.U. for the second half of 1959. In the Glasgow survey the average for the first half of 1960 was 2·3 S.U. compared with 2·5 S.U. for the whole of 1959. The highest single value of strontium 90 recorded in 1960 was 6·6 S.U.; in 1959 the highest figure was 9·5 S.U.

Medicine and the Law

"Incurably of Unsound Mind"

A WIFE petitioned in June, 1960, for divorce on the ground of the husband's incurable unsoundness of mind. The husband, by the Official Solicitor as his guardian *ad litem*, denied the allegation.

The marriage took place in 1936. There were three children, now all over the age of 16. In 1948, the husband, then aged 40, was certified to be of unsound mind, the diagnosis being paranoid psychosis with persecutory delusional ideas. He was admitted to a mental hospital and remained an inpatient until he discharged himself in August, 1960, two months after the divorce petition had been filed. While in hospital, the husband had had no special treatment except drug therapy. On his discharge, he returned to the matrimonial home, but lived entirely separate from the wife. He lived and slept in one room, doing everything for himself, including cooking. The wife refused to live with him, taking the view that he was still "mental".

The medical superintendent of the hospital in which the husband had been from 1955 until he discharged himself said that in his opinion the husband was not cured, or curable, in the sense that his mental state could be returned to what is normal and average for the population, without the aid of drugs; he had been prescribed "Largactil" and while he took that drug he was sane, but if he ceased to take it he would in all probability again become insane. The husband's family doctor said that in his opinion, the husband was not grossly disturbed mentally, and was capable of managing his affairs.

Mr. Commissioner LATEY, Q.C., said that there was no statutory definition of the phrase "incurably of unsound mind" or of "unsoundness of mind". The opinions of doctors on whether a person was of unsound mind, or on whether a condition was incurable, had to be given due weight, but the court had to decide these matters on all the facts of the case. The phrase "of unsound mind" had in the past been accepted by the court in its ordinary, somewhat indeterminate, meaning, in the case of anyone lawfully certified as such. But that yardstick had now gone. There was no longer any certification containing the phrase "of unsound mind", though detention might still be ordered or continued in suitable cases, under the Mental Health Act, 1959. Having regard to recent legislative policy of extending the range of voluntary patients and of de-certifying certified patients, it might well be that a large proportion of mental patients, whether voluntary or certified, did not come within the category of persons incurably of unsound mind, for the purposes of divorce.

1. Medical Research Council Monitoring Report Series no. 2. Assay of Strontium-90 in Human Bone in the United Kingdom. Results for 1960, Part I, with some further results for 1958 and 1959. H.M. Stationery Office. Pp. 1s. 3d.

The husband had given evidence, and had been cross-examined. During the hour or so that he was in the witness-box, he showed not the slightest sign of mental disorder of any kind. He was clear, thoughtful, and logical in his answers and gave every appearance of being a sounder witness than many parties in matrimonial causes. His Lordship accepted the husband as a reasonable man and a truthful witness and a person fully qualified to manage his own affairs, and, if permitted, to resume married life. He respected the sincerity of the opinion of the medical superintendent, but was not persuaded by it. He could not find that the husband was incurably of unsound mind, or even that he was of unsound mind. The petition therefore failed and must be dismissed.

Webb *v.* Webb. *Probate, Divorce and Admiralty Division: Mr. Commissioner* Latey, Q.C. July 31, 1961. Counsel and solicitors: R. J. A. Temple, Q.C. and Neil Taylor (W. B. Blackwell & Co.); James Comyn, Q.C. and B. H. Pearce (Official Solicitor).

D. R. ELLISON
Barrister-at-Law.

An Employer's Duty

THE plaintiff, a young woman, had been employed for five years in a factory where component parts of bicycles were manufactured. Her work involved contact with grease, to some of the ingredients of which her skin was susceptible. In April, 1956, she developed dermatitis on both hands. On May 14, when she returned to work with a clean certificate from her doctor, she was offered and accepted other work, assembling driving sleeves, which involved her handling parts which had come through a bath of lubricating suds (which contained some oil) but which had passed through a drying chamber before reaching her. Her employers regarded that work as the driest available in the factory. On three further occasions during 1956 she again developed skin trouble; but each time she returned to work, after absences of some weeks, she accepted work on the assembly of driving sleeves and continued to do it until the middle of January, 1957, when it became possible for the employers to transfer her to the only other suitable work available. She again developed dermatitis in 1959. She sued her employers for damages alleging that she had contracted dermatitis as the result of their negligence or breach of duty in that, knowing that she had suffered from dermatitis, they had permitted her to continue on work which involved contact with lubricating suds, which they knew or ought to have known were irritant and likely to exacerbate or cause dermatitis. The trial judge found that the employers had been negligent and awarded her £480 damages. The employers appealed.

Lord Justice SELLERS said that no breach of duty could have been established in respect of the first attack of dermatitis. When the plaintiff returned to work in May, 1956, she was anxious to get work and the defendants gave her the best they had. She had accepted it without protest. If she had not taken it she could not have worked at all. He could not believe that the common law required employers to refuse to employ a person who was willing to work for them simply because they thought that it was not in that person's best interests to do that work. That would be imposing a restriction on the freedom of the individual wholly foreign to the common law. There was no duty at common law requiring an employer to dismiss a person rather than to retain him and allow him to obtain his wages. The duty on the employer here was to have all reasonable care having regard to the fact that the plaintiff had had dermatitis. Applying that standard, the evidence did not establish any breach of duty. The appeal should be allowed.

Lord Justice DEVLIN, agreeing, said that there was no legal duty on an employer to prevent an adult employee from doing work he or she was willing to do. If there was a slight risk, it was for the employee to weigh it against the desirability or necessity of the employment. The relationship between employer and employee was not that of schoolmaster and pupil. There was no duty on the employer to offer alternative safe employment and no obligation on him to dismiss an

employee rather than allow him to take a small risk. The duty implicit in the judge's finding did not exist and the finding must be set aside.

Lord Justice DANCKWERTS agreed.

Withers *v.* Perry Chain Co. *Court of Appeal:* Sellers, Devlin, and Danckwerts, *L.JJ.* July 21, 1961. Counsel and solicitors: David Croom-Johnson, Q.C., and Philip Owen (Clifford Turner); H. E. Hooson, Q.C., and B. Griffiths (Evill & Colman).

E. M. WELLWOOD
Barrister-at-Law.

Consummation of Marriage

A HUSBAND petitioned for a decree of nullity of marriage on the ground that the marriage had not been consummated, owing to the wife's incapacity to consummate it, by reason of a structural malformation consisting of the complete absence of a vagina. The wife denied the incapacity alleged.

The marriage took place in 1955, the husband being then 23 and the wife 21. In 1951, the wife had been seen by a gynæcologist, who advised her that she could never menstruate or bear children, but that if she ever wanted to marry, an operation was possible to make an artificial vagina. For the first year of the marriage, there were sexual relations of a kind, on an average of three times a week, but as time went on, their frequency decreased. In September and October, 1958, the gynæcologist again saw the wife; by that time, however, quarrels had become frequent between the parties and, early in November, 1958, the husband left the wife and had never returned to her. The gynæcologist formed the opinion that the chances of a successful operation to create an artificial vagina were good, but that after the husband had left the wife the operation was no longer advisable, unless there were to be a resumption of cohabitation accompanied by sexual intercourse. The wife was willing to have the operation.

Mr. Justice KARMINSKI said that at the time the husband left the wife and at present the wife was incapable of full sexual intercourse, but if the operation had been performed, it would in all probability have enlarged or created a vaginal passage, enabling the husband to penetrate much further than ever before and to achieve a large degree of sexual satisfaction, and the wife to achieve a degree of satisfaction.

The question therefore arose as to what, in law, constituted consummation. In D. *v.* A., in 1845, it was laid down that if there was a reasonable probability that the wife would be made capable of *vera copula*, that was, of natural coitus, though without power of conception, the marriage could not be pronounced void; but that if she was not, and could not be made, capable of more than an incipient, imperfect, and unnatural coitus, the marriage should be pronounced void. It was important to note that medical science did not, in 1845, provide a remedy for the condition under consideration. Those principles had now to be applied in the light of the considerable advances made by medical science in the last 100 years. In B. *v.* B. [1955] P. 42, it was stated, *obiter*, that the fact that the wife had an artificial vagina would negative the possibility of *vera copula*. His Lordship dissented from that view, it being, in his judgment, possible for a marriage to be consummated, in law, where the wife had had created for her an artificial vagina.

The real question for the court to answer was whether consummation was practicable or impracticable. On the evidence, this wife could have been made capable, by means of an operation, of a sufficient degree of sexual intercourse to amount to *vera copula*. As she was willing to undergo that operation, his Lordship was unable to find that consummation of the marriage was impracticable. The husband's petition therefore failed and must be dismissed.

Symonds *v.* Symonds (orse Warren). *Probate, Divorce, and Admiralty Division:* Karminski, *J.* June 29, 1961. Counsel and solicitors: W. R. K. Merrylees (Few & Kester, Cambridge); J. D. F. Moylan (Ginn & Co., Cambridge).

D. R. ELLISON
Barrister-at-Law.

In England Now

A Running Commentary by Peripatetic Correspondents

I DO like these new diagnostic sliderule things. Mine is saving me literally minutes each day. Time which until now was spent foolishly cudgelling two failing Betz cells, has now become miraculously available for more positive work, like filling in certificates. For instance, a chap came to see me the other day complaining of perennial cough, worse in winter, copious mucoid sputum turning green in nasty weather, and dyspnœa; smoked 40 a day. Was I stuck, or was I? Then I thought of your friend and mine, Superdiagnostex, lying in the cupboard where I hurled it reflexly when a salesman left it on trial last month. Feverishly I fed into it the symptoms as the patient repeated them. Hypnotised and with a sense of mounting excitement I watched the instrument at work. With devastating logic it seized in its inhuman way on the respiratory system, inexorably eliminated a collagen disease or two, then in a flash of pure deductive wizardry revealed the answer in all its devilish simplicity: CHRONIC BRONCHITIS. Tears of gratitude blinded me as I wrote up an E.C.10. Some of the strangest illnesses are beginning to crop up in the practice now, which, but for Superdiagnostex, might have lurked insidiously for years; things like carapato disease, subacute cholera, and, once, coccidioidomycosis. It's a wonderful invention. To my mind it also has one big advantage over more conventional methods of differential diagnosis. It can be manipulated discreetly and silently, behind a desk at knee-level, while former methods always involved turning over pages of books and much cross-reference work. The new method preserves the patient's confidence and the physician's dignity.

* * *

When I bought them, I imagined my car safety-belts would serve as a salutary reminder of human fallibility, and lead in the end to better driving. Alas, they don't and they haven't. The main effect so far, apart from acute torticollis from trying to reverse down the drive with the darn thing in position, has been a striking tendency towards just that kind of driving which I once affected to despise.

My Corncrake Six leaves something to be desired on the corners, and when I took the turn at the hotel at any speed above the legal maximum, I used to land in my wife's lap, with the kids in a heap on the floor. Securely trussed to the seat, I can now take the corner at fifty-five with nothing more alarming than a faint smell of burning rubber from the tyres. My wife doesn't ask for a lift into town any more, and the kids are demanding danger money.

The T-junction at the vicarage, which used to merit a timorous exit into the main road, is now tackled with euphoric abandon which has earned three near-misses to date. I can't help it—it's just not possible to lean far enough forward to see past the parson's laurels.

As for the old dears who leap on to the pedestrian crossing at the Square, who worries if the scream of my tyres sets their adrenaline flowing? My liver is now immune from damage caused by the rim of the steering wheel.

Anyone like to buy a nice safety-belt, cheap? It's far too dangerous for me.

* * *

The hungry cockroach comes as close to an omnivore as one is likely to find. It will nibble the red cells off an unstained blood-smear and is capable of biting in half an object as small as a dried flattened erythrocyte. Although I believe cockroaches are prepared to eat whole books at a pinch, they seem primarily attracted to the covers. On my bookshelves they have not sampled all volumes; some have been severely attacked while others are untouched. The nibbling is confined to the outer cuticle, and the underlying cloth is undamaged, though roughened and dull. There must be a chemical basis for this form of literary taste, and I would guess that it may be the use of a gelatinous size.

Your publication *Principles of Medical Statistics* ranks high among their preferences. Other volumes in which my cockroaches (*Blatella germanica*) have shown particular interest are the *Yearbook and Guide to Southern Africa*, *Yearbook and Guide to East Africa* (both published by Robert Hale, London), *Microscope Design and Construction* (Cooke, Troughton, and Simms, York), and *Cancer Progress 1960* (Butterworth Medical Publications). Colour seems unimportant, as this list includes blue, red, and black, but, it may be noted, no greens.

It would be invidious perhaps to mention those books which are less palatable, but it is interesting that in general these are the publications of the more prolific medical firms—e.g., Churchill, Saunders, Lewis, Henry Kimpton, Williams and Wilkins, Butterworth (green volumes). Is it possible that they guard some important secret?

I approach you therefore as one of the edible publishers in the hope that the common ingredient may be traced and avoided. The benefits to tropical statistics may be greater than you think. Superficial value judgments by the consumer often carry more weight than they ought.

* * *

He came in as a not very serious attempted suicide, a curly-haired blond Fenman of the deepest simplicity. Why had he done it then? His prospective father-in-law didn't like him, objected among other things to his riding a motor-cycle without a licence, not to mention marrying his daughter. Why hadn't he a licence? Couldn't he buy one? Well, you see, he'd had an accident, one or two in fact. (After four casualty admissions he had had to own up to having fits.) They wouldn't give him a licence any more now. But he didn't see why he shouldn't ride his motor-bike still. Did his father-in-law know why he hadn't a licence? No. So his father-in-law didn't know about the fits? Well, no. Did his fiancée know then? Well, not exactly. You see, he didn't want to tell her in case, if she knew, the babies might have fits too.

* * *

My tour of Australasia was sheer joy, and a great experience marred by one minor incident. The car in which I was travelling turned off the side of the road and, travelling at fair speed, looped the loop, expectorating me into the undergrowth at the end of the loop. After a time two agricultural workers arrived on the scene (I was about to say "pedestrians", but there really aren't any left in Australia); then the police; then a large car out of which appeared a gentleman in a soft hat who looked as if he had stepped straight out of *Highway Patrol* in the T.V. series. "Have you sent for the ambulance, Fred?" he asked, and on being answered in the negative, unhooked a mouthpiece from inside his car and said briefly, "Better send it, Jim. Two mild ones." This 50-yard-range assessment of prognosis, and probably diagnosis also, impressed and cheered me.

* * *

"Doctor," said Old Mother Brown solemnly, "I've Got Sugar." "Very well, save me some of your water, and we'll see if you've got sugar," I replied in my special soothing-voice-for-deluded-patients. In due course I tested her urine. The Benedict's turned bright orange at once. I returned to Mother Brown. "How", I asked her, "did you know you had sugar?" "The Home Help told me." When I met the Home Help I asked her how she knew the old lady had sugar. "It was the mats," came the cryptic reply. "How do you mean, the mats?" "Well, one of my other old ladies is diabetic, and both she and this old lady have a little difficulty, sometimes, holding their water, you know; so it was the mats."

Two morals, one that the unduly large number of flies in the house should have reminded me of the mellitus in diabetes mellitus, and the other that those poor doctors in hospitals cannot fall back on the Home Help Diagnostic Service.

* * *

The operation was being carried out under local anæsthesia. The surgeon had made two burr-holes, and had evacuated a large subdural hæmatoma. He was syringing the space with normal saline when suddenly the patient said "Doctor, would you call this brain-washing?"

Letters to the Editor

LOCAL-HEALTH-AUTHORITY CLINICS

SIR,—At the recent British Medical Association meeting at Sheffield, Dr. G. E. Crawford, of Liverpool, is reported[1] as saying: "Let the Minister turn his axe to local-authority clinics, which are a complete anachronism". Dr. Crawford was advocating this line of action in an attempt to stop putting the prescription charges up from 1*s*. to 2*s*. The extra shilling would bring in about £10 million in a year, which is slightly more than the total cost per annum of all local-health-authority antenatal and child-welfare clinics.

The National Health Service, in the year ended April, 1959, cost a total of £671 million, this sum being made up as follows:

	£ million
Hospital and specialist services	383
General medical services	66
Pharmaceutical services	69
General dental services	46
Supplementary ophthalmic services	14
Local-health-authority services	59
Other costs (doctor's compensation, superannuation payments, &c.)	34

It is very easy to advocate drastic amputations of the service in an attempt to show savings, or avoid increases, but whatever action is taken must be on realistic lines, not purely empirical grounds, particularly when the action is by members of the medical profession.

If we are to effect savings in the total cost of the National Health Service we must, once again, tackle on a realistic basis the question of prevention of illness and injury. Take one example only—home and other accidents. If they were reduced by 10% this would show a saving of approximately £50 million on hospital and consultant services. If all doctors set out to prevent illness instead of concentrating on treating end-results our drug bill could be reduced by possibly £18 million in five years. Dental caries is a field for prevention by the medical and dental profession with consequent saving of millions of pounds a year on the Service.

Let us all, therefore, foster in every way preventive medicine whether the measures be small or large. In my opinion, local-health-authority child-welfare and antenatal clinics provide an educational and supervisory service of the best kind, with a valuable preventive content.

Modern antenatal and child-welfare clinics can be so arranged that their services are complementary to the services provided by general practitioners. This has been done in this county after consultation with the local medical committee to the advantage of patients, general practitioners, and the local health authority.

My plea is not to cut out the few preventive facets of the National Health Service but to redouble our efforts to increase, by every possible means, all preventive aspects of medicine. In this way, we would be doing a real service to the community by keeping people healthier and, at the same time, reducing the total cost of the National Health Service by several million pounds a year.

Mold. G. W. ROBERTS.

ERADICATION OF TUBERCULOSIS

SIR,—As a whole-time worker in this field I am much interested by the report last week of the conference held at the Institute of Diseases of the Chest. While it is encouraging to be able to take an optimistic view of the situation as it is in this country, it is perhaps over-optimistic to think that what is still to be done can properly be called "mopping-up operations". It would surely have been better if some reference had been made to the necessity to continue the urgent prosecution of the search

1. *Times*, July 19, 1961.

for new cases even though the effort is subject to the law of diminishing returns. The price of freedom from tuberculosis is eternal vigilance. If we relax now the old dragon will rise to strike again.

Hawkmoor Chest Hospital,
Bovey Tracey,
Devon.

R. L. MIDGLEY.

TREATMENT OF LICHEN PLANUS

SIR,—I was interested in the correspondence (July 29) on lichen planus. Becker and Obermayer [1] classified it under neurodermatoses. Many dermatologists [2–6] stress the importance of psychological factors in skin diseases.

MacKenna very artistically described neurodermatosis when he stated that " in some cases the skin is an organ of stress which bears the brunt of nervous agitation, acting as the canvas on which perturbation of the mind is painted, or as an organ of relief into which the turbulence of the mind can safely be poured ".

A man of 39, who had lichen planus for thirteen months, was referred to me for hypnotherapy. A dermatologist told him that it was a " stress disorder "; and it proved resistant to every form of treatment.

It began while he was in the Far East. At first his wrists and the back of his hands were affected; then it gradually spread all over his body.

He admitted he was sensitive, selfconscious, moody, a perfectionist, and an anxious, worrying type. " During the four months while I was away I was continually worrying about my wife and children."

He proved to be amenable to hypnotherapy; and after four sessions over a period of two months all the lesions cleared up except two small patches on the back of his left wrist. Though still present, two years later, these no longer bother him.

London, W.1. A. P. MAGONET.

PSYCHOLOGICAL TRAINING FOR FUTURE MIDWIVES

SIR,—I should like to make a few observations on Dr. Le Vay's letter (July 29).

In the first place, midwives in this country cannot be dismissed as mere " ancillary workers ". Whether one approves or not, in the British system they frequently act as " principals "—that is to say, the primary and most operative relationship of many patients is with one of them. While they bear this responsibility, and unless or until the system is altered, they must be treated as responsible people.

Secondly, I have to admit that my experience of psychiatrists is limited. I therefore never dreamt that any one of them, charged with the task of helping to enlighten midwives, would be so lacking in commonsense as to do this in such a way as to put " weapons " into their hands; would not take the trouble to re-acquaint himself with midwifery to the point of knowing the rashness of attributing long labour to any purely psychological cause; would not take for granted (as simple, non-expert observers do as a matter of course) that with any teaching such as that proposed it is the assistance given to the participants in dealing with their own reactions that is the most important.

For the past fourteen and a half years I have worked (full-time) in an obstetric unit in which psychiatrists, who are members of the team, have played an increasing part. Their teaching has been informal, some of it even casual, but it is quite clear that the ability of the staff—midwives and doctors—to handle patients has become steadily easier and more effective. These facts may or may not be related, but at least the influence of the psychiatrists has not been harmful; and to all of us it has seemed to be very helpful indeed. But as I have said, I had not realised that our psychiatrists have been so exceptional.

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London, W.C.1. SHÎLA RANSOM.

1. Becker, S. W., Obermayer, M. E. Modern Dermatology and Syphilology; p. 180. Philadelphia, 1947.
2. Sneddon, I. B. *Brit. med. J.* 1949, i, 472.
3. Shorvon, H. J., Rook, A. J., Wilkinson, D. S. *ibid.* 1950, ii, 1300.
4. MacKenna, R. M. B., MacAlpine, I. *Lancet*, 1951, i, 65.
5. Russell, B. *Med. Pr.* 1956, **235**, 176.
6. Ritter, E. C. *Practitioner*, 1956, **177**, 598.

PSYCHIATRIC SEQUELÆ OF CHRONIC EXPOSURE TO ORGANOPHOSPHORUS INSECTICIDES

SIR,—I wish to comment on the article by Dr. Gershon and Professor Shaw (June 24). In lieu of any plausible evidence, they offer a neat combination of post-hoc reasoning, speculative generalities, and imaginative interpretation of published data to support their premise that a history of handling organophosphorus insecticides establishes a causal relationship between these compounds and a garden variety of psychiatric problems. The paucity of the factual data that are presented and the liberal use that is made of them raise a question about the objectivity of this article. Some of the more conspicuous deficiencies of this paper are as follows:

(1) Although 13 of 16 local physicians in fruit-growing districts thought that mental ill health and depression had not increased and were not more prevalent among orchardists, " the findings of a small field survey suggested that psychiatric disorders might be commoner in fruit-growing areas than in towns ".

(2) In the title and throughout the text, the term " exposure " is repeatedly used to denote handling of organophosphorus insecticides, yet nowhere is the slightest attempt made to describe the alleged exposures or define what is meant by the term. *Handling of* and *exposure to* toxic chemicals are not synonymous. Yet, " 16 cases of chronic exposure have been investigated ".

(3) " So far we have seen 16 cases." 16 cases of what? In only 7 was the diagnosis made by a psychiatrist. One may conclude that the psychiatric diagnoses in the other 9, including the cases of headache, fatigue, and impaired memory, were made by the authors, who specialise in pharmacology. It would be interesting to know something about the evaluation that the psychiatrists gave of the 7 cases which they saw and how the other 9 cases came to the attention of the authors.

(4) The paper offers only brief summaries of 4 of the cases. With a topic of such great potential significance, the reader is entitled to the salient features of all of the cases, especially because of the ubiquity of many of the symptoms to which the authors attach so much importance.

(5) " He showed mild symptoms of poisoning intermittently over the four years " and " eleven had had acute poisoning with the classical signs and symptoms ". These poisonings evidently are the authors' retrospective diagnoses for: (*a*) there is an implication that in at least 1 case the physicians in actual attendance held other views; and (*b*) there may be some difference of opinion among informed persons as to how classical were the " classical signs and symptoms " which the authors cited. In this connection, the text leaves some doubt as to whether the authors ever saw the patients they are reporting.

(6) The observation that " the effects on the central nervous system are not so well known " (an understatement) is followed by an imposing list of symptoms. It is not clear whether this list is drawn from other sources, or represents merely the authors' conclusions. If it is drawn from the literature, it is so at variance with accepted fact that it should be documented by references.

Ordinarily a paper of this kind would not merit comment, for undoubtedly the scientific community will relegate it to its proper resting-place. In this case, I feel constrained to write a protest for the substance of this paper had wide publicity in Australia, including the public

press, before it appeared in *The Lancet*, and, following publication, it was disseminated in abstract form over the wires of international news services, presumably to be reproduced in newspapers, magazines, and other media throughout the world. It would be surprising indeed if this did not result in an increased incidence of illness of the type which Gershon and Shaw claim to " have been produced by organophosphorus compounds ".

Personnel Division,
American Cyanamid Co.,
New York.

H. H. GOLZ
Director of Industrial Health.

" BREACH OF CONTRACT "

SIR,—When Dr. Dyke (July 8) inveighs against the insolent power of committees and tribunals set up by Government to investigate, try, and sentence his colleagues in cases of alleged breach of contract, he deserves our support.

Lest it be thought that such counsel is wrong-headed, if not subversive, I will remind you of the words of Blackstone—towards whom such epithets are not usually directed—in chapter 23 of his Commentaries, where he says, among many other apposite and good things, " It is upon the whole, a Duty which every man owes to his country, his friends, his posterity, and himself, to maintain, to the utmost of his power, this valuable Constitution in all its rights; and, above all, to guard with the most jealous circumspection against the introduction of new and arbitrary methods of trial, which, under a variety of plausible pretences, may in time imperceptibly undermine this best preservative of English liberty ".

Lowton, near Warrington,
Lancashire.

W. H. LYLE.

A LEG-DRESSING TROLLEY

SIR,—Most general hospitals now have a leg clinic. Since 1929, when ambulatory pressure bandaging was taught us by Mr. Dickson Wright, it has steadily proved itself. Twenty to thirty patients need their bandages changing in an average clinic. This is time-consuming, for the old bandage must be removed, the leg cleaned, and new dressings and bandages applied.

Sister O. Matthews of the London Homœopathic Hospital and myself have devised a bandaging trolley to save time. On it instruments, lotions, dressings, and various medicated, adhesive, and extensible bandages are immediately to hand. It has been in service for two years and has been copied and used at two other hospitals, where experienced sisters have confirmed its convenience.

It is made by Messrs. Chas. F. Thackray, Ltd., of Park Street, Leeds.

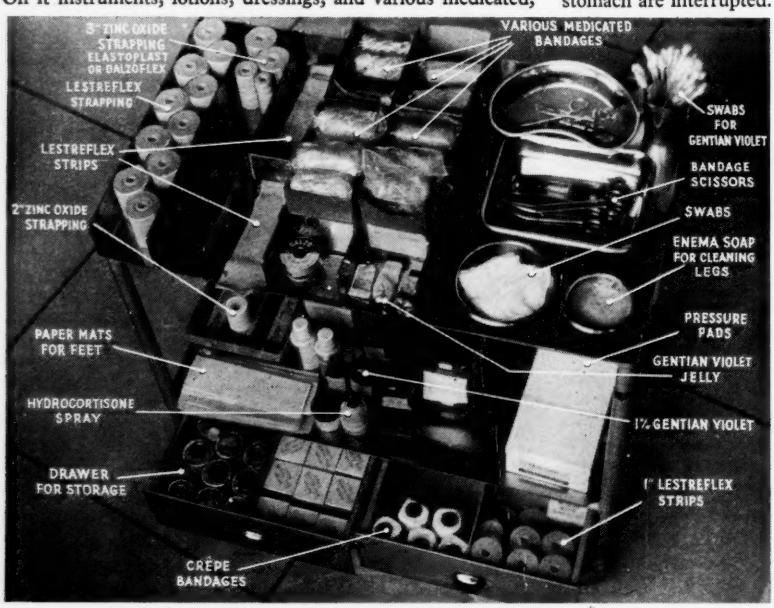
London, W.1. HAROLD DODD.

ILEUS AND POSTOPERATIVE INTESTINAL MOTILITY

SIR,—I have read with great interest the preliminary communication by Professor Wells and his colleagues (July 15). Their observations bear out in full my own findings, which have led me to feed my gastrectomy cases postoperatively by intestinal tube.

Many years ago, during a partial gastrectomy, I observed peristaltic activity in the small bowel. This peristalsis was present even in the vicinity of the anastomosis being performed. I saw this again many times. This made me think that the view that peristaltic activity was absent in the bowel when the abdomen is opened (and subsequently in the postoperative period) was not strictly correct. I then realised that, in a partial gastrectomy, a tube placed in the bowel beyond the anastomosis through which fluid could be administered would be a much better way of replacing fluid loss than intravenous infusion. To confirm this, I passed a small tube into the bowel beyond the anastomosis. Through this I injected a small amount of a barium suspension; and on subsequent X-ray examination, the radio-opaque solution was seen to have reached the lower reaches of the small intestine in about six hours. Next, I devised a double tube, the larger element of which was for aspirating the stomach. The smaller element projected six to eight inches beyond the larger and was for intra-alimentary administration of fluid. At first I gave only water into the intestine, but my practice now for some years has been to give a ' Casilan ' drip feed. I agree entirely with Professor Wells and his colleagues when they write, " with modern anæsthetic sequences intestinal movements may not cease during even major abdominal operations ", and again, " different parts of the gastrointestinal tract behave differently in these respects, the small intestine being the most active, and the stomach and colon the most static ". The stomach remnant after a partial gastrectomy is an inactive bag devoid of peristaltic activity; this is because, in a gastrectomy, the nerves to the stomach are interrupted. After a time tonus returns, but I do not know exactly when. One of my patients actually had acute dilatation of the stomach after a partial gastrectomy.[1] Colonic distension is agreed to be due to gas; and the old practice of passing a flatus tube is worth while, even if only a little gas is expelled. The patient's relief when flatus is automatically discharged is considerable.

Professor Wells and his associates also write: " Jejunal feeding can be substituted for intravenous feeding in selected cases." This, I believe, is better for several reasons. In the first place, the bowel selectively absorbs fluid, whereas with an intravenous drip the body has to take in what the surgeon administers, and it is easy to overload the body with fluid. There is a risk of waterlogging the lungs; and a patient with an intravenous drip set up cannot move about, and hence his circulation-rate is lowered. When casilan is given as an intra-alimentary drip, not only



1. Lee, M., Somerville, E. *Brit. med. J.* 1941, i, 751.

is the lost fluid replaced, but in addition valuable potassium, sodium, and other ions are given which help to prevent post-operative ileus. Giving a high-protein diet is important in the postoperative period when protein loss is great. It is true, as Professor Wells and his associates state, that diarrhœa may be caused in a few cases fed by intra-alimentary drip; but this clears up as soon as the drip is stopped.

I believe that administration of fluids into the bowel after abdominal operation is the safest and most physiological method. The double tube I have devised [2] makes it easy to apply; and at the same time it allows the stomach to be kept empty in the postoperative period when it is static and empties slowly. Furthermore, the intra-alimentary tube passing through the anastomosis after a partial gastrectomy, whether it be of the Billroth I type (stomach anastomosed to duodenum) or the Hofmeister-Finsterer operation (stomach remnant to jejunum) safeguards the anastomosis until healing is well under way. This applies particularly to the Billroth I operation, in which the stoma often becomes œdematous and temporarily obstructed.

London, W.1. MAURICE LEE.

CLINICAL TEST OF 6-AZAURIDINE

SIR,—We are writing to ask for assistance in a clinical test to determine whether 6-azauridine (AzUR) is effective treatment for trophoblast tumours.

We have recently reported [3] that AzUR given orally is an effective ovicide in the mouse, terminating early pregnancy at dosage levels which produce no detectable toxic effect in the mother. We have found that the first effect of the drug on the fœtus is to reduce its rate of growth, and to produce a relatively structureless mole. Later, there is autolysis, beginning at the centre of the mole, rapidly progressing to the periphery, and eventually including the placenta. Within a few days of the onset of lysis, the products of conception are entirely resorbed and normal œstrous periodicity is resumed. Though we do not yet know the effect of AzUR on the human ovum, we do know that it is non-toxic in man in doses which, by analogy, might be expected to be ovicidal. Thus, it has been given in doses of 300 mg. per kg. body-weight daily for several weeks in leukæmia, without any of the adverse effects commonly produced by cytotoxic and cytostatic agents such as mercaptopurine and folic-acid antagonists.

Supplies of AzUR are limited by the difficulty of preparation. Moreover, we have found that different batches vary somewhat in activity, and their ovicidal activity and their toxicity are not necessarily related. However, the Distillers Company (Biochemicals), Ltd., have undertaken to supply AzUR in amounts which, though small, will be sufficient to determine its activity against trophoblast tumours. Each batch will be prepared in aqueous solution for intravenous use, and will then be tested in mice both for ovicidal activity and toxicity.

It is proposed that suitable batches of AzUR shall be available at the Highlands Hospital for patients under the care of Mr. David Savage. It is hoped that physicians and surgeons will refer cases of trophoblast tumours, especially chorion carcinoma, so that they may be considered for inclusion in the trial. The numbers will be determined by the amount of AzUR available; it is hoped that this will become sufficient for the inclusion, later, of some cases of hydatiform mole. Inquiries concerning admission should be addressed to Mr. David Savage, F.R.C.S., Highlands Hospital, London, N.21.

MARGARET A. SANDERS
B. P. WIESNER
JOHN YUDKIN.

Department of Nutrition,
Queen Elizabeth College,
London, W.8.

2. Lee, M. *Post Grad. med. J.* 1957, **33**, 78.
3. *Nature, Lond.* 1961, **189**, 1015

LANGUAGE: THE LOST TOOL OF LEARNING

SIR,—For a long time it has been necessary for a spokesman of Sir George Pickering's eminence to criticise in forthright fashion the deplorable situation into which the professional (and other) language of doctors has fallen. We are greatly in his debt. Other voices have been raised from time to time but have been ignored, or made inaudible by the grinding of jargon's juggernaut.

The situation is serious and not just the preoccupation of pedants and pitiable colleagues on the lunatic fringe. For, as we think and speak so do we act if we are in good faith; if our thought and speech are confused and obscured so will be our acts—and, among other things, this means our research and approach to patients.

To look back, for example, at medical papers and books towards the end of the last century is to find writing which, though perhaps wordy by present-day standards, is clear and precise. No doubt, no wondering what on earth the man means. It is a prodigious irony, in the Age of Science when Man supposes he is clarifying all branches of knowledge, that doctors (we must speak only of ourselves, for it is the disorder in our own house that is nearest to us), when professionally engaged, talk and write chaotically. Surely it is disconcerting to read medical articles full of the machinery of precision —statistics—only to be confounded by the text.

Unnecessary neologisms, one suspects, feed on and bolster personal pride and are not easily set aside; and, of course, they are used by everybody else. But pride apart, is it not easier, readily understandable, more euphonious, companionable and only five letters more to write "high blood-potassium", than it is to write "hyperkalæmia"? Errors of logic arise from ignorance of its rudiments and, while Sir George is disposed to blame the medieval Schoolmen for being "the greatest of all obstacles to the growth of new knowledge won by the scientific method", there is little doubt that recollection by present-day medical doctors of Thomist-fostered principles of logic and disputation would make their own talk and writings considerably clearer—to say the least.

When sitting down to write case-sheet or dissertation it is well worth remembering the simple rules which appear on the first page of chapter I in Fowler's *The King's English*:

> "Prefer the familiar word to the far-fetched.
> Prefer the concrete word to the abstract.
> Prefer the simple word to the circumlocution.
> Prefer the short word to the long.
> Prefer the Saxon word to the Romance".

The poet can ignore these rules, for his craft involves the love of words and their precision; the doctor writing Medicine ignores them at his and other men's peril.

It is really rather sad we have to be reminded that Medicine is a fusion of "two cultures". That this is no longer generally felt is due to a widespread misapprehension that Science is replacing the Art of Medicine instead of being, as it is, its tool—no matter how important a tool, still a tool.

It is even sadder that these things need to be said at all.

Cardiff. W. RAYMOND PARKES.

SIR,—I agree with Sir George Pickering (July 15) that no unnecessary new words should be introduced, but I think he is overemphasising the facts. It is difficult to understand how you can work without tools; if the tools have been lost, as Sir George says, how can it be explained that knowledge—the natural result of learning (and to learn you need the Lost Tools)—is today wider than ever before?

What is wrong with medical jargon? Every branch of knowledge has it; or does he want new, popular names to all the rare and little-known names used in legal, military, mechanical, and

other jargons? I am sure that the treatment would be worse than the disease.

Obviously "nephrosis" has little meaning to the outsider, but every doctor should know it. What popular names can be given to nephritis, nephron, or nephritic—all terms closely related to nephrosis and widely recognised and understandable? The result would be a new Esperanto, spoken and written by nobody.

Besides, there are always national differences; Sir George refers to the undertaker and his American counterpart, the mortician. It is regrettable that countries of the same language use different names for the same thing; still, it is a little disconcerting that Latin and Greek words are pronounced the same in almost every Latin country, yet they are pronounced completely differently in English.

And certainly a candidate should not fail simply because of a few grammatical mistakes (often unintentional in a fight against time); or would you rather be treated by a doctor just because he writes perfectly? I certainly would not. If Sir George's strong views were applied, we would lose many good doctors, lawyers, and so on.

I think it would be better to suppress the proper names applied to diseases and symptoms, and replace them by common specific names as far as possible; everybody understands "tuberculosis", but not all know "Koch's disease," to give one of the simplest examples. If anyone wants to know names, there is always a *History of Medicine*.

To avoid further confusion, the best thing would be to create an Academy of Language: they have existed for a very long time in most European countries, and they are the authorities for the correct grammatical rules and the correct use of new words

Middlesbrough General Hospital. J. M. SANCHEZ.

COMBINED REQUEST AND REPORT FORM

SIR,—In many hospitals much work is involved in making out laboratory request forms, in typing reports, and in storing them, both in case-notes and laboratory files. This is particularly tiresome in a busy ward or a laboratory (often incompletely staffed) dealing with many daily requests for prothrombin estimations the results of which are only of ephemeral value.

To reduce the amount of writing, typing, telephoning, and filing of requests and/or reports of this sort, we designed a card (see below) which is a combined request form, report form, and prescription sheet. Its size makes it suitable for inclusion in the case-notes when the patient is discharged from the wards; and it is of a distinctive colour to make for easy identification (our cards are 8 in. wide by 11½ in. long, and printed in black on a pale Lincoln green). The printing in the large rectangle (top left) is the same as the heading on our ordinary request and report forms except for the inclusion of "diagnosis".

Specimens are collected and sent with the completed card (or the card only when the laboratory staff collect the specimen) on the morning of the last day for which the dose of anticoagulant has been written up. In the pathology-department office the specimen is numbered, details entered in the day-book in the usual way, and the specimen number entered on the card, which is then passed on to the laboratory with the specimen. The technician writes the result on the card, keeping a copy in the laboratory work-book. All the cards are then returned to the wards (with a note of the dosage when the hæmatologist is responsible for this) later the same day. No typed reports are sent; no filing has to be done in the department office: there are no flimsy reports to be lost in the wards or stuck into the case-notes; there is no telephoning to the ward.

This system has given complete satisfaction for the past two years to clinicians, ward sisters, and laboratory staff. The back of the card is also used, and there is enough space for several weeks' prescribing.

Lincoln Area Department of Pathology, County Hospital, Lincoln. J. R. H. PINKERTON DOREEN GILBERT.

THOUGHTS ON TREATMENT

SIR,—Mr. Gervis's protest in his splendid letter of June 17 against the "habitual expectation of medicine" should not be confined to the English, for this syndrome is just as common and as virulent in other loci of the affluent society.

Analysis of the ætiology of the syndrome is usually directed to an attack on the stressful pace of modern life or to the affirmation that the "tremendous strides" taken by modern medical science have outstripped in two decades the learning which had accumulated during the previous two centuries.

There are two other ways of viewing iatrogenic neurosis. Firstly, with the increasing division and narrowing of the specialties we doctors are prone to attacks of delusions of grandeur, sometimes believing that our treatment has resulted in rather than coincided with an improvement in our patients' condition. Such an attitude of mind can only lead to intellectual myopia which is hardly an "advance in medicine". Secondly, the manufacture and distribution of pills and potions is one of the most lucrative businesses on record, resulting in many cases of a profit of several hundreds or even thousands per cent. The barrage of glossy advertisements fired at medical practitioners must surely result eventually in the disintegration of their powers of reasoning which can hardly be to the benefit of the patients under their care.

Two apocryphal remarks of William Osler may be relevant to this approach—firstly, that the primary duty of the physician is to protect his patients from taking medicines, and secondly, that if all the drugs in the Pharmacopœia were thrown into the sea it would be better for humanity but worse for the fishes. Such statements seem irreverent and even impolite when viewed in the context of modern medical practice. Nevertheless in our

ANTICOAGULANT DOSAGE CARD

Patient's Surname and Christian names in full — Hosp. Reg. No. — Sex — Date of birth

Diagnosis

Ward and Hospital or Home Address — Consultant or Practitioner

This card is a combined request form, report form and prescription sheet. It should be sent with a specimen of patient's blood—1·8 ml. in the special prothrombin bottle with the green printed label—to the hæmatology laboratory on the morning of the last date on the card. The doctor asking for the tests should sign here: _____

Specimen No.	Date	Prothrombin Index	Anticoagulant	Dosage instructions and Doctor's signature	Checked by

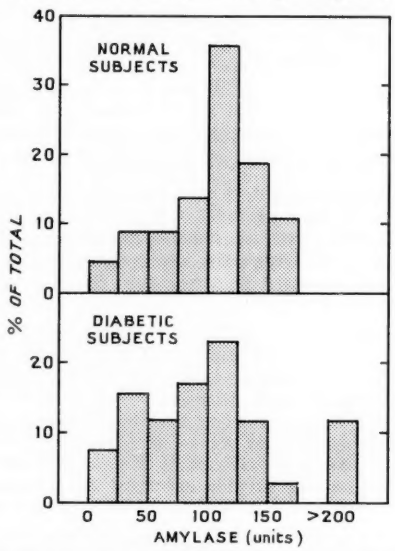
enthusiasm for treatment there can be no harm in refreshing our memory with the fact well recognised by our forebears in the Dark Ages of Medicine that the only predictable phenomenon of life is death. In persuading our patients of this truth perhaps kindness is more potent than potions?

Canberra, Australia. S. B. FURNASS.

SERUM-AMYLASE LEVELS IN DIABETES MELLITUS

SIR,—Serum-amylase measurements remain important in the diagnosis of acute pancreatitis; but there is much uncertainty about the activity of this enzyme in other diseases. In diabetes mellitus, for example, some workers maintain [1–3] that serum-amylase values are raised, while others [4 5] conclude that enzyme activity is usually abnormally low. More recent studies [6] suggest that serum-amylase activity in diabetic patients is within normal limits.

Unexpected rises in serum-amylase may at times complicate clinical evaluation. We have, therefore, attempted to establish



Amylase activity in sera from 48 healthy subjects and 178 diabetics.

the range of amylase activity in a randomly selected diabetic population. A new amyloclastic technique [7] which yields results in the equivalent of Somogyi units has been used to measure amylase activity in sera from 48 clinically healthy subjects and 178 patients with diabetes mellitus (see figure). In the healthy group, serum-amylase values did not exceed 175 units. Approximately 70% of these subjects exhibited activities between 75 and 150 units. In the diabetics, on the other hand, there was a wider dispersion, values ranging from 0 to 600 units. Little more than 50% of the diabetic group had amylase activities between 75 and 150 units. It is noteworthy that of 4 patients with severe metabolic acidosis 2 exhibited amylase values within normal limits, while in the other 2 enzyme activity exceeded 500 units. Enzyme activity was measured in 3 patients on several occasions (see table). Serum-amylase values of 600 and 450 units were observed in case 1 during an episode of severe metabolic acidosis. Little or no enzyme activity was found in serum specimens obtained 11–13 days after the onset of acidosis. Likewise, cases 2 and 3 showed appreciable fluctuations in serum-amylase activity during apparently well-controlled periods.

SERUM-AMYLASE LEVELS IN 3 DIABETICS

Case no.	Date (March, 1961)	Amylase (units)	Case no.	Date (March, 1961)	Amylase (units)
1	3	600	2	15	330
	4	450		20	85
	14	0			
	15	0	3	20	175
	16	20		22	295

These data suggest that diabetics may have extremely high, normal, or low serum-amylase values. Furthermore, activity of the enzyme may change relatively rapidly and unpredictably in diabetics. Inasmuch as the physiological function of serum-amylase is unknown it is difficult to attach clinical significance to alterations of the enzyme in diabetes mellitus.

This investigation was supported in part by grants from the American Osteopathic Association (project T-1602), the United States Public Health Service (project A-4609), Baxter Laboratories, and the Attending Staff Association of the Los Angeles Osteopathic Hospital.

Los Angeles County Osteopathic Hospital, College of Osteopathic Physicians and Surgeons, Los Angeles, California. RONALD L. SEARCY
JAMES M. DUNN.

1. Myers, V. C., Killian, J. A. *J. Biol. Chem.* 1917, **29**, 179.
2. Reid, E., Myers, V. C. *ibid.* 1933, **99**, 607.
3. Reid, E., Quigley, J. P., Myers, V. C. *ibid.* p. 615.
4. Somogyi, M. *ibid.* 1940, **134**, 315.
5. Huggins, C., Russel, P. S. *Ann. Surg.* 1948, **128**, 668.
6. Street, H. V., Close, J. R. *Nature, Lond.* 1957, **179**, 164.
7. Peralta, O., Reinhold, J. G. *Clin Chem.* 1955, **1**, 157.

A SOAPLESS SERVICE?

SIR,—Of late there has been discussion in high places of certain public services, the charge made for them, and the method of ingress to the premises. The turnstile, it would seem, is anachronistic and abhorrent.[1]

There is a related deficiency of more concern to our profession. Many public conveniences designed for women lack facilities for washing the hands. Whilst running water and handbasins are usually provided, soap and handtowels very often are not; when they are a charge is made for their use, which is proportionately too high to encourage this simple but important public-health measure. The criticism applies equally to certain theatres and restaurants, blameless in other respects.

It is unconscionable that hygiene in public places should be allowed to fail for want of disposable paper towels, and regrettable that women should be obliged to add tablets of soap to the cosmetic impedimenta already in their handbags.

Department of Bacteriology, Charing Cross Hospital Medical School, London, W.C.2. ROSALINDE HURLEY.

DRUG ADDICTION

SIR,—I am impelled to write by Dr. Stungo's letter of July 22. I must support most strongly Dr. Chazan's assertion that "there may be more addicts than we think," whether it can be sustained on the facts of her letter or not. Nor can I agree with the definitions quoted. My dictionary (Oxford) gives "addict" as "devote . . . apply habitually (*to* a practice)". And to me there is no distinction between addictions and habituation (what an ugly word!).

In my limited experience there are many habitual eaters of drugs, all of whom show withdrawal symptoms in some degree, even with such reportedly innocuous preparations as barbiturates. 'Drinamyl', which combines dexamphetamine and a barbiturate, is an obvious offender; but even the "sleeping tablet" is not innocent.

There are too many people in this country with a "psychic and physical dependence" on a habit-forming drug. They cannot lead a "normal" existence without it; and do not necessarily need increasing doses. To use a separate category of "dangerous drugs" may be useful administratively, but should not prevent the recognition of a drug that is dangerous.

1. See *Lancet*, July 29, 1961, p. 272.

Finally, I suspect that the "addicts known to the Home Office" are habitual takers of substances covered by the D.D.A. regulations.

Cardiff. H. CAIRNS.

ACTION OF HEPARIN IN ISCHÆMIC HEART-DISEASE

SIR,—The hitherto unpublished information provided by Dr. Sharp (June 24) on the detailed properties of the agent responsible for the viscous metamorphosis of platelets is extremely interesting in providing more evidence in favour of a new coagulation factor.

The properties of this agent appear to be identical with those of the antiheparin principle present in serum. The possible clinical importance of the serum-heparin antagonist arises from the demonstration of in-vivo and in-vitro heparin resistance in patients with recently established thrombosis,[1–3] and the physiological role of heparin as an anticoagulant.

It remains to be established whether the antiheparin principle of serum is an ætiological factor in thrombus formation or merely a byproduct of the thrombotic process. The demonstration of increased factor-VII activity in the plasma of patients with recently established thrombosis [4] raises a similar problem. Factor VII also is a serum factor which resembles the antiheparin activity in being present in excess in clotted blood; and this too might be released into the circulation from a formed thrombus.

Wessler and Reimer [5] have in fact been able to show that the agent present in serum which produces rapid thrombosis in experimental animals resembles in physical properties the antiheparin activity and the viscous metamorphosis activity of serum; but there is an important distinction. The American workers found their thrombotic principle was absent from Christmas disease (factor-IX deficient) serum. In my experiments the sera from cases of severe Christmas disease showed appreciable antiheparin activity although it was less than normal.

—	Anti-heparin activity of Poller [7]	Viscous metamorphosis activity of Sharp [8 9]	Thrombogenic serum factor of Wessler and Reimer [5]
Present in serum ..	Yes	Yes	Yes
Excess in serum (i.e., activated during clotting)	Yes	?	Yes
Stable on storage ..	Yes	?	Yes
Absorbed from serum by alumina or barium sulphate ..	Completely	Yes	Yes
Present after platelet-free clotting ..	Yes	?	?
Reduced by oral anti-coagulant treatment	No	No	No
Present in Christmas (factor-IX deficient) serum	Yes (confirmed [6])	Yes	No
Neutralised by heparin	Yes	Yes	Yes
	Not likely to be due to Hageman factor and/or plasma-thromboplastin antecedent owing to different physical properties	Present in plasma-thromboplastin antecedent serum	Absent in Hageman serum; diminished in plasma-thromboplastin antecedent serum

As these properties of serum appear of importance I have tabulated the physical properties of the three serum agents.

Dr. Sharp expressed the view that the three properties of serum—antiheparin activity, viscous metamorphosis activity, and thrombogenic activity—may be due to one factor, a factor probably distinct from any known coagulation factor. The antiheparin properties and viscous metamorphosis activity do not appear to belong to any known agent in serum; but, unless the differences in the thrombogenic activity of serum are found to result from the use of the artificial animal experimental system, it seems likely that more than one new factor is needed to explain these differing activities of serum. All three activities may be important in the pathogenesis of thrombosis.

Withington Hospital, West Didsbury, Manchester. L. POLLER.

1. Crafoord, C. *Acta chir. scand.* 1937, **79**, 407.
2. Waugh, T. R., Ruddick, D. W. *Canad. med. Ass. J.* 1944, **50**, 547.
3. Poller, L. *Angiology*, 1954, **5**, 21.
4. Poller, L. *J. clin. Path.* 1957, **10**, 345.
5. Wessler, S., Reimer, S. M. *J. clin. Invest.* 1960, **39**, 262.
6. Niewiarowski, S., Węgrzynowicz, Z. *in* Thrombosis and Anticoagulant Therapy (edited by Wm. Walker); p. 72. Edinburgh, 1961.
7. Poller, L. *J. clin. Path.* 1960, **13**, 226.
8. Sharp, A. A. *Lancet*, 1961, i, 1405.
9. Sharp, A. A. *Brit. J. Hæmatol.* 1958, **4**, 28.

SHORTAGE OF RADIOGRAPHERS

SIR,—May I suggest that the introduction of a grade of radiographers of more limited training might be of assistance? I suggest that these girls have one year's training in anatomy and radiography only.

I have spoken to a number of girls who have told me that at one time they were interested in doing radiography but did not embark on the course because they felt they would be unable to reach the standard of physics required in the final examination.

Whittington Hospital, London, N.19. J. A. MONTGOMERY.

DIAGNOSIS OF CARBOHYDRATE-INTOLERANCE DIARRHŒAS BY STOOL CHROMATOGRAPHY

SIR,—Recently, cases of diarrhœa have been reported which are caused by a deficiency of the sugar-splitting enzymes lactase, invertase, maltase, and amylase.[1–9] This form of diarrhœa disappears promptly when the sugar concerned is excluded from the diet, or if the missing enzyme is added to it.

For the diagnosis of diarrhœa caused by lactose, maltose, or sucrose intolerance, the sugar-loading curves and the lactic-acid content of the stools are useful; and, with some difficulty, such an intolerance can be detected.

Aminoacids in infants' stools have been investigated; but sugar chromatography has not, so far as we know, been performed. We carried out the following chromatographic method to detect disturbed absorption of sugars. Stool supernatant fluid 1 vol., sodium hydroxide (0·3 *N*) 2 vol., and zinc sulphate (5%) 2 vol. are centrifuged; suitable amounts of supernatant fluid are transferred to chromatographic paper. The solvent employed was ethyl acetate/pyridine/water (12/5/4); the location reagent was aniline-diphenylamine; 20 ml. of solution (aniline 1 ml., diphenylamine 1 g., and acetone to 100 ml.) is mixed with 0·6 ml. *m*-phosphoric acid and used immediately.

The test-result was positive in one case of lactose intolerance, and in several others caused experimentally by simultaneously feeding small doses of lactose and calcium gluconate; while chromatographic investigation was negative in 20 cases of diarrhœa of non-metabolic origin.

If there was an absolute deficiency of lactase, only lactose was found in the stool chromatographic patterns; while if the enzyme deficiency was partial, the respective monohydrates were also found.

P. DURAND
G. Gaslini Institute, Genoa, Italy. A. M. MARTINO.
University Institute of Hygiene, Genoa. G. M. LAMEDICA.

1. Darling, S., Mortensen, O., Sondergaard, G. *Acta pædiat., Stockh.* 1960, **49**, 281.
2. Durand, P. *Minerva Pædiat.* 1958, **10**, 706.
3. Durand, P. *Probl. act. Pédiat.* 1959, **4**, 496.
4. Durand, P. *Pédiatrie*, 1960, **15**, 407.
5. Fois, A., Vedovini, F., Marinello, E. *Acta pediat. lat., Parma*, 1960, **13**, 596.
6. Holzel, A., Schwarz, V., Sutcliffe, K. W. *Lancet*, 1959, i, 1126.
7. Jeune, M., Charrat, A., Cotte, J., Fournier, P., Hermier, M. *Pédiatrie*, 1960, **15**, 411.
8. Inall, J. A. *Proc. R. Soc. Med.* 1960, **53**, 318.
9. Weyers, H. A., van De Kamer, Y. H., Dicke, W. K., Ysseling, Y. *Acta pædiat., Stockh.* 1961, **50**, 55.

INTENSIVE-CARE UNITS IN AMERICAN HOSPITALS

SIR,—In answer to Dr. Buxton Hopkin (July 8), I should say that I by no means intend to convey the impression that intensive-care units in the United States are replacing postoperative recovery rooms. In no instance I am aware of has a recovery room been replaced by an intensive-care unit.

Unfortunately his statement, "although these units (intensive-care) are rapidly becoming a feature of all American hospitals . . ." is far from accurate. Of some 7000 hospitals in this country it is most unlikely one could find intensive-medical-care units in more than 10%. From a recent search we have made I am certain there are less than 100 intensive-surgical-care units.

As Dr. Buxton Hopkin points out, visiting is a problem in the intensive-care unit. For that *specific* reason our unit, and many others, are designed not as an "open ward" but as a series of small private rooms arranged in either circular or square (double corridor) manner. We have found our three "family rooms" a great convenience to visitors faced with a long bedside vigil, as they have a nicely appointed lounge to relax in when they would otherwise stand in the way of doctors or nurses working with the patient.

It comes as a surprise to our nurses that they "become frustrated because as soon as a critically ill patient is over the worst he returns to the division; the nurse loses touch, thus missing the sense of vocational fulfilment which arises from nursing a moribund patient back to early convalescence." Often they maintain informal follow-up contact, either directly with the patient and family or through word-of-mouth communication with sister nurses. The common feeling of our intensive-care nurses is that they have provided skilled care at the most critical time, often spelling the difference between life and death, and that in meeting this challenge they are indeed achieving the high ideals of their profession.

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DONALD C. CARNER
Administrator.

RECOGNITION OF THE FEEBLE PULSE

SIR,—Recognition of feeble arterial pulsation is often bedevilled by the sensation of pulsation in one's own fingertips.

The usually recommended solution is to contrast the two pulse-rates by counting the radial pulse-rate in the palpating hand with the free hand. This is not always an easy manœuvre and may be impossible in certain circumstances—e.g., when palpating tissues at operation which may contain small arteries.

It is much more convenient to palpate one's own pulse in the free hand. This can easily be done by palpating the lateral digital branch of the princeps pollicis artery (see accompanying figures). A little practice may be required (and a few people do not have a sufficiently prominent digital vessel); but I have found it to be a manœuvre well worth acquiring.

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W. KEITH YEATES.

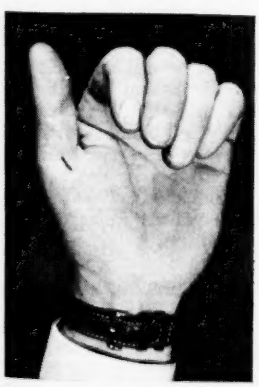

Fig. 1—Site of lateral digital branch of princeps pollicis artery.

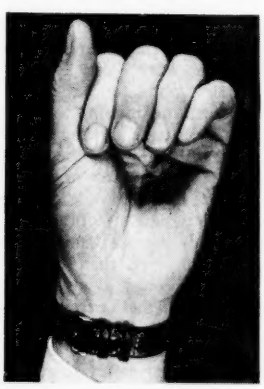

Fig. 2—Palpation of the artery.

COMBINED AND SINGLE-DRUG THERAPY IN MALIGNANT BLOOD-DISEASE

SIR,—Combined chemotherapy of acute leukæmia with 6-mercaptopurine plus corticosteroids gave a higher remission-rate than that observed for either of these administered alone.[1] In the same disease synergistic effects have been noted with combined therapy with folic-acid antagonists plus adrenal steroids.[2] Synergism was not observed with other drug-combinations given for malignant blood diseases.[3–5]

TABLE I—SINGLE-DRUG THERAPY

Acute leukæmia	Chronic myeloid leukæmia	Chronic lymphatic leukæmia	Hodgkin's disease
Folic-acid antagonists (3114 cases)	Busulphan (1264 cases)	Radioactive phosphorus (896 cases)	Nitrogen mustards (4246 cases)
Corticosteroids (2269 cases)	Radioactive phosphorus (1071 cases)	Nitrogen mustards (762 cases)	Tretamine (925 cases)
Mercaptopurine (2027 cases)	Nitrogen mustards (673 cases)	Tretamine (704 cases)	Antibiotics (794 cases)
Nitrogen mustards (373 cases)	Urethane (620 cases)	Corticosteroids (209 cases)	Corticosteroids (312 cases)

In table I are recorded the chemicals which an exhaustive search of original literature reveals as the most frequently tried in acute leukæmia,[6] chronic granulocytic and chronic lymphocytic leukæmia,[7] and Hodgkin's disease.[8]

Table II shows the drugs most often given together in the same four blood diseases. The large number of patients with acute leukæmia who have received combined chemotherapy is

TABLE II—COMBINED THERAPY

Acute leukæmia	Chronic myeloid leukæmia	Chronic lymphatic leukæmia	Hodgkin's disease
Mercaptopurine (1922 cases)	Nitrogen mustards (92 cases)	Nitrogen mustards (131 cases)	Corticosteroids (138 cases)
Corticosteroids (1806 cases)	Urethane (88 cases)	Urethane (61 cases)	Nitrogen mustards (128 cases)
Folic-acid antagonists (1142 cases)	Corticosteroids (68 cases)	Tretamine (41 cases)	Vitamins (20 cases)
Azaserine (402 cases)	Radioactive phosphorus (32 cases)	Corticosteroids (26 cases)	Antibiotics (16 cases)

striking. It is interesting that the same three chemicals should have been used most frequently in both single-drug and combined therapy of acute leukæmia but in exactly the reverse order, with folic-acid antagonists ranking first in single-drug procedure and third with multiple drugs. I was surprised to find fewer than a hundred patients with acute leukæmia treated by combined therapy with nitrogen mustards, which rank fourth in single-drug therapy.

Three chemicals repeat themselves in both single-drug and multiple-drug therapies of chronic granulocytic leukæmia, chronic lymphocytic leukæmia, and Hodgkin's disease, but the number of trials with each is much smaller than in acute leukæmia. One wonders why in chronic myelocytic leukæmia busulphan, which ranks first in single-drug therapy, has been

1. Sampey, J. R. *Chemother. Rev.* 1961, **2**, 7.
2. Sampey, J. R. *Amer. J. Pharm.* 1961, **133**, 148.
3. Sampey, J. R. *Int. Rec. Med.* 1961, **174**, 297.
4. Sampey, J. R. *Amer. Practit.* (in the press).
5. Sampey, J. R. Unpublished data.
6. Sampey, J. R. *Int. Rec. Med.* 1960, **173**, 312.
7. Sampey, J. R. *Amer. J. Pharm.* 1960, **132**, 145.
8. Sampey, J. R. *ibid.* p. 27.

tried by only two investigators for combined chemotherapy. Equally striking is the lack of any report on the use of radioactive phosphorus in combined chemotherapy of chronic lymphatic leukæmia, when this is most often administered for single-drug therapy of the disease. Tretamine should prove effective in combination with other drugs in Hodgkin's disease, since it ranks second in single-drug therapy; yet I have found only three reports of trials of combined therapy with this drug.

Multiple-drug therapy only rarely increases toxicity. While synergism has not been as frequent as was hoped, and the delay in drug resistance has been more difficult to assess, multiple-drug procedures do not appear to increase the dangers of cytotoxic and cytostatic drugs.

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JOHN R. SAMPEY.

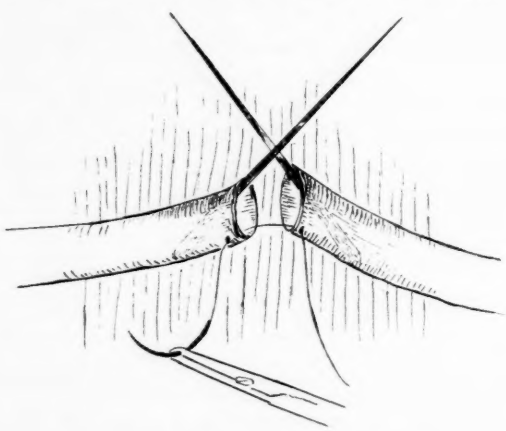
REPAIR OF A SEVERED PAROTID DUCT

SIR,—Injuries which sever the duct of the parotid gland are uncommon. Repair is not easy; and failure will result in a salivary fistula. A balance must be struck between the hazards of stricture of the duct when too many sutures appose the cut ends, and leaking of saliva when too few are put in.

I record 2 cases in which parotid ducts divided by a knife injury were surgically repaired.

The identification of the cut ends of the duct may be difficult as the duct is the same colour as the surrounding structures. The blunt end of straight needles can be passed into the lumen of each to confirm their identity.

To place the sutures accurately two straight needles introduced as above (blunt end first) were passed for a quarter of an inch into each lumen; the shafts of the needles were then crossed and lowered till the cut ends of the duct were apposed



Method of anastomosing a severed parotid duct.

(see figure). Three sutures of arterial silk were inserted symmetrically in the duct end. The needles were then removed, and the overlying skin wound was closed. Three sutures were enough to appose the ends of the duct accurately and ensure healing without stricture formation and prevent saliva leaking.

CASE 1.—A Sinhalese man was admitted to the General Hospital, Colombo, on April 14, 1961, with multiple injuries after an assault. He had several deep incised wounds, and had hæmorrhage and shock. After preliminary resuscitation, his injuries were cleansed and sutured under a general anæsthetic. One of these wounds was a horizontal incised wound on the face running from in front of the lobule of the right pinna to a point above the angle of the mouth midway between it and the ala of the nostril. The parotid duct had been divided. The cut ends of the duct were apposed as described above. A fluid swelling formed over the site of the anastomosis and reached the size of a marble. Saliva leaked from a pin-head sinus in the skin wound on April 26, and the swelling deflated. The sinus healed on May 1, and the swelling did not recur.

CASE 2.—A woman was admitted to the same hospital in December, 1934. She had an incised wound and the right parotid duct had been cut. The duct was repaired as described and healed soundly.

This technique seems to achieve good results in repairing cut parotid ducts; and convalescence is less stormy. [1 2]

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MILROY PAUL.

EXCITEMENT RELATED TO HYPERBILIRUBINÆMIA

SIR,—A single man, now 38 years old, was transferred here from Hellingly Hospital in January, 1960, to be nearer to his blind mother so that he could be visited and go on leave more easily. He had been jaundiced from birth. 2 brothers died in the first month of life, 1 at least with jaundice. The 3rd is alive and well although he may be slightly jaundiced at times. The mother had a nervous breakdown lasting three years, two years before the patient was born.

The patient's mental illness began insidiously in his early twenties and took the form of recurrent attacks of excitement, variously described as schizophrenic and manic at different times. These attacks had necessitated his admission to Hellingly Hospital on four occasions, and were separated by long periods of quiet cooperative reserve when he was occupied and spent a lot of time reading. During these long periods there were shorter and less obvious ones of dejected, disinterested, somnolent, apathy. The excited phases were characterised by garrulousness, restlessness, and hallucinations, as well as cheerfulness and untidiness of person.

When the patient's jaundice was being investigated here, a series of serum-bilirubin levels were estimated, and during this series he happened to have one of his periods of excitement. We were stimulated to review this patient recently by Prof. C. H. Gray and interested to note on doing so in retrospect, that the patient's excitement coincided with a relatively speaking low serum-bilirubin level.

	Serum-bilirubin (mg. per 100 ml.)		
Date	*Direct*	*Indirect*	*Total*
1960			
April 13	0·40	9·00	9·40
April 26	0·40	9·80	10·20
May 25	0·83	5·12	5·95
June 1	0·95	9·80	10·75
June 23	1·02	14·64	15·66
June 30	0·80	10·40	11·20
August 13	0·92	7·63	8·55
1961			
June 21	1·02	14·48	15·50

The table lists all the bilirubin levels available, and the dates on which they were estimated. The patient was excited between May 2 and 15, 1960, judging from the medical and nursing notes, and there was also an isolated entry by the medical and nursing staff on Aug. 30, 1960, that the patient was overactive and too bright on that day. Since that date he has exhibited no further excitement apart from very occasional fits of giggling or smiling to himself; but he did have an episode of depression for a few days in October, 1960.

The patient's jaundice proved to be of the group to which Gilbert's disease belongs, but with distinctly higher serum-bilirubin levels than are reported in that condition, and yet, in the absence of other factors, levels insufficiently high to cause abnormal central nervous system signs such as are seen, for example, in kernicterus. We wondered, therefore, whether the levels reached in this patient who revealed no abnormal central nervous system signs or unequivocal intellectual deterioration on psychological testing, might still have been

1. Rossi, D. *Oral Surg.* 1959, **12**, 1419.
2. Boyer, H. E. *J. oral Surg.* 1960, **18**, 248.

sufficient to interfere with the metabolism of brain cells most closely related to the emotional state, since these have been considered particularly sensitive to interference with metabolic processes. The fact that relatively speaking low rather than high levels of serum-bilirubin were associated with excitement, however, at first appeared paradoxical.

Meyer [1] has found that damage to anterior hypothalamic nuclei can produce excitement, presumably by releasing the posterior group—with which they are normally in balance [2 3]—to uninhibited activity. In our patient therefore it would be necessary to postulate that high bilirubin levels affect the metabolism of the posterior hypothalamic nuclear group more than they do their anterior counterparts, but not sufficiently to cause irreversible changes which would prevent a rebound to excitement on release from such levels. It is interesting in this connection to note that of the hypothalamic nuclei, Claireaux [4] only mentions the mammillary bodies as showing excessive staining with bilirubin in such patients, and these bodies are in the posterior hypothalamus. Exhibition of trifluoperazine hydrochloride (' Stelazine ') mg. 5 b.d. had little effect on the excitement in our patient, although the basal ganglia, which may be the site of action of this drug, are amongst the structures most liable to be affected by the discoloration. This seems to add force to the view that hypothalamic nuclei were the important ones in our patient's behaviour, since the distribution of lesions can vary from patient to patient.

Finally we should like to refer to the recent paper of Ackner and his coworkers (June 10), since bilirubin and porphobilinogen appear to be in the same biochemical sequence. Although no direct relationship was in fact discovered between the mental states in Ackner's patients and the various phases of their acute porphyria, it was nevertheless thought that there might be some undiscovered connection with the series of metabolic events in question.

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B. CATES
J. P. CRAWFORD.

ONCOLYTIC EFFECTS OF A STREPTOMYCETE NOT PRODUCING ANTIBIOTICS

SIR,—I have previously described [5 6] oncolytic effects from streptomyces fermentation products and stated that these effects were obtained only with antibiotic-producing strains. That statement now needs correcting. Oncolytic effects in man have been demonstrated for a species which elaborates no antibiotic: Tendler's thermophilic actinomyces 401.[7]

I consistently maintained that cytotoxic, radiomimetic, or " non-competitive antimetabolite " qualities were not only unnecessary but actually undesirable in an oncolytic designed for use in man; and I was interested in the reports of the screening on animal tumours, conducted by the Cancer Chemotherapy National Service Center on Professor Tendler's material, which showed exceptional in-vivo activity but absolutely no in-vitro cytostatic effect. An attempt to elicit antibiotic activity in this broth revealed the reverse; it *stimulated* the growth-rate of a wide variety of unicellular organisms.

We had been previously giving dried *Streptomyces griseus* beer, later mycelium, and then a polynucleotide concentrate from the latter, as an " anabolic " in (surgically and radiologically) abandoned cancer patients. Since the properties of Dr. Tendler's broth coincided with those of streptomyces products in common use,[8] I tried its effect on 5 patients who had been adjudged " inoperable ". My trial was conducted to decide: " does it shrink the tumour ?"

Detumescence was observed in 3 of the 5 patients in the trial. These patients had obstructive gastrointestinal neoplasms.[9] Furthermore the response was unequivocal and occurred in the first week. In all patients there was a granulocytosis, whether the broth was given orally or intramuscularly; and the lassitude, nausea, or generally harmful effects usually encountered with cytotoxic agents were absent.

The surviving patients are being maintained on the desoxyribonuclease/ribonuclease digest of *Str. griseus* mycelium which is easier to obtain at present, being a by-product of streptomycin manufacture, than the small amounts available of any of the broths being produced for the National Program.

When we observed a marked rise in granulocyte count within 24 hours in the 2 patients receiving intramuscularly 2 ml. of broth concentrated twentyfold (roughly 800 times the dose found effective in mouse tumour 180), we suspected that we were dealing with a polynucleotide (" nucleic acid ") effect. We assayed nucleic-acid content. This was 3 to 5 times that of our currently employed *Str. griseus* broth. Many oligonucleotides and polynucleotides stimulate the growth of protozoans, but none exceeds in its effect the nucleotides from streptomyces species.[8] We conclude that since the oncolytic effects described for streptomyces materials are concentrated along with the nucleotide fraction, that the nucleotides are the active constituents.

If this conclusion is correct, the present search through thousands of streptomyces fermentations for protoplasmic poisons is in the right place, but for the wrong thing. Psicofuranine, a nucleoside isolated from a variety of *Str. hygroscopicus* has a marked antineoplastic effect in rats, none in mice, and is not tolerated by man. But it is absolutely devoid of cytotoxic properties.[10] Digests of thymonucleic acids have been reported to inhibit spontaneous mammary adenocarcinoma in C3H mice. In this instance a stimulation of certain nonspecific immunity factors by nucleotides is invoked [11]; and the older literature attributes such virtues to countless yeast nucleic-acid preparations, many of which are still obtainable on prescription.

In 1951, both the *Str. griseus* and the *Str. aureofasciens* I was using were shown to inhibit senile C3H mammary cancer; these tumours may be more comparable with those in man than the transplanted type in animals. The psicofuranine episode [10] shows the prohibitive species difference to obtain even among rodents.

A large variety of mould products have been reported effective in cancer in man, from myxomycetes to streptomycetes.[12] It is known that fragments of foreign ribonucleic acid can " transduce " bacteria and that virus nucleoproteins take over the communication facilities of helpless cells for self-replication. All streptomyces species can form aerial hyphæ and thus must have this " information " at their disposal. This information may be unique to streptomyces; it consists of a sequence of nucleotides. Short strips of information are transposable, as in bacterial transduction.

Our studies are proceeding on the theoretical basis [13] that certain peculiar nucleotide sequences liberated by or from streptomyces may be utilisable by higher living forms. They may function as " punctuation ", and alter reproductive or protein synthetic activity, this could be advantageous, just as an appropriate period, comma, or participle can make an otherwise incoherent sentence intelligible.

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ROBERT D. BARNARD.

1. Meyer, A. *J. Neurol. Psychiat.* 1944, **7**, 66.
2. Crawford, J. P. *Med. Pr.* 1960, **244**, 525.
3. Crawford, J. P. *ibid.* 1961, **245**, 139.
4. Claireaux, A. E. *Brit. med. J.* 1960, i, 1528.
5. Barnard, R. D. *Lancet*, 1951, i, 1157.
6. Barnard, R. D. *ibid.* 1954, ii, 604.
7. Tendler, M. D. Dissertation, Columbia University, N.Y. 1957.
8. Lentnek, A., Bath, P. E., Barnard, R. D., Coren, O. J. *in Proc. 5 Int. Congr. Nutr.* Washington, 1960.
9. Gehan, E. A. *J. chron. Dis.* 1961, **13**, 346.
10. Evans, J. S., Gray, J. E. *Antibiot. and Chemother.* 1959, **9**, 675.
11. Braun, W. *in Amer. Cancer Soc. Seminar.* St. Petersburg, Fla., 1961.
12. Natenberg, M. The Cancer Blackout. Chicago.
13. Ireland, F. H. Personal communication.

Parliament

Crimes of Violence

Mr. DAVID JAMES, raising on the adjournment the question of protecting the public against crimes of violence, pointed to the fivefold increase in such crimes since the late war. He complained that not enough people were being segregated under section 72 of the Mental Health Act, 1959: surely the principle must be that the wicked go to prison and the sick go to hospital. He urged that psychopaths should, as in Denmark, receive an indeterminate sentence. As regards medical evidence he suggested, first, that this should be the property of the court, and, secondly, that it should be brought in every case involving violence of more than a certain degree. He was convinced that psychopaths should be kept under penal conditions. Prisons should be organised on a factory basis; for, to redeem a man, we should make him work and pay him the full rate for the job to enable him to recompense the victim. The pressure on prisons might be relieved by adopting the Continental system of the suspended sentence in some cases. Mr. James would like to see revived the concept of the penal colony—for he was appalled at the prospect of a person being put behind bars for a long time—and the Western Isles of Scotland might provide suitable sites.

Mr. KENNETH ROBINSON recalled that the Royal Commission on the Law relating to Mental Illness and Mental Deficiency had insisted that psychopathy should be regarded as a medical disorder; and treatment or training of the psychopath could not suitably be applied in a prison setting. Not much was agreed about psychopaths, but one thing on which almost everyone agreed was that prisons made them worse.

Mr. CHARLES FLETCHER-COOKE, joint under-secretary of State for the Home Department, did not believe that there was evidence that a high proportion of the crimes of violence was committed by unstable persons who could not be deterred from offending again by any of the penalties available to the courts. The paramount consideration was protection of the public. He did not think it would be right to widen the definition of psychopathy—certainly not yet. As to indeterminate sentences for crimes of violence exceeding a certain degree, he held that the public would not tolerate such an inroad into the liberty of the subject. With regard to the proposal for medical experts to provide the courts with evidence, this would tend to usurp the functions of the courts. The general public was always very loth to give the power of decision to experts; and he himself had noticed that experts invariably disagreed. He fully agreed that leaving psychopaths in prison with ordinary prisoners had a very bad effect. The proposal to establish prisons in the Western Isles was impracticable since prison officers and their families (as had been found at Dartmoor) wanted to be in touch with ordinary urban civilisation. On the subject of turning prisons into factories, Mr. Fletcher-Cooke declared that it would be quite wrong to pay prisoners full wages unless their work and output justified this; and unfortunately at present overcrowding in prisons, the need for security, the shortage of staff, and many other factors made it impossible to bring prison industries up to the standard which would provide an economic basis for paying full wages. But with the therapeutic value of a long, good, hard, and productive day's work nobody would disagree.

Birmingham Maternity Hospital

IN an adjournment debate, Mr. DENIS HOWELL said that Birmingham Maternity Hospital, which was one of the teaching group of hospitals in the city, had lately decided that it would admit 300 fewer cases a year. This decision, which had the effect of casting an increased burden on neighbouring regional-board hospitals, had been reached without consultation with these hospitals or with the regional board. When he had asked the Minister of Health what communication had taken place between the teaching-hospital group and the regional hospital board, he had been told that it was not in the public interest to disclose communications between these two bodies. He had long suspected that the teaching hospitals in Birmingham were tending to divorce themselves from the social needs of the community.

Miss EDITH PITT, parliamentary secretary to the Ministry of Health, said that at the Birmingham Maternity Hospital the average number of births per month had risen from 159 in 1955 to 206 in 1959 and 223 for the first ten months of 1960. At this average the pressure on the hospital and its staff could no longer be safely maintained. The decision to reduce forward bookings had been reached also for the safety of patients. Moreover this decision was necessary if the hospital was to continue to accept all emergencies referred to it. Miss Pitt denied that she had said it would not be in the public interest to disclose what consultations had taken place between the two hospital authorities: she had said that such disclosure would not be in the interests of the hospital service, and this she reiterated.

Mr. KENNETH ROBINSON said that there had apparently been a total failure of communication between the teaching hospital and the regional board. If the boards of governors wanted to jeopardise the autonomy of teaching hospitals, they should continue to behave in the way that the governors of the United Birmingham Hospitals had done in this instance. Planning the hospital services in its region was probably the most important function of a regional hospital board; and it could not carry out this function unless it had proper liaison and proper consultation with the board of governors of the teaching hospitals in its midst.

Industrial Injuries

When the Consolidated Fund (Appropriation) Bill came up for its third reading on Aug. 1, Mr. HAROLD FINCH, opening a debate on industrial injuries, said that thirteen years' administration of the National Insurance (Industrial Injuries) Act had revealed many anomalies and injustices. Foremost among the causes of dissatisfaction was the matter of pneumoconiosis. The so-called simple stage of the disease was divided into three categories, each with a recognised pattern on a radiograph. When a man was placed in category 1 medical boards not only did not make an award but they went to the extent of telling a man that he did not have the disease. He might leave the board in the belief that he had no dust on his lungs. In the interests both of safety and of health men should be told when they had even a small degree of dust retention. The Act should be reviewed and many of its clauses remodelled, although the framework was sound.

Mr. RICHARD SHARPLES, Joint Parliamentary Secretary to the Ministry of Pensions and National Insurance, said the definition of pneumoconiosis had been laid down in the Act and it would require an amending Act to change it.

The Minister of Pensions and National Insurance, Mr. JOHN BOYD CARPENTER, referred to the question of a man examined by a pneumoconiosis panel and placed in radiological category 1—that is, found not to have pneumoconiosis but to have some dust on the lung or some other condition. This was a difficult problem and the Minister was anxious to deal with it. It might be possible to evolve a formula that did relate specifically to pneumoconiosis and did not purport to give a medical opinion on the state of the lungs from other points of view. He had been in consultation with outside bodies and he hoped to meet some of the difficulties.

QUESTION TIME

Handicapped Refugees

Mr. H. E. RANDALL asked the Home Secretary what decision had been made to curtail the extension of the United Kingdom scheme for handicapped refugees entering the country.—Mr. R. A. BUTLER replied: More than 1100 refugees have been accepted for residence here as a result of the schemes announced during World Refugee Year. Apart from a few residual cases now under consideration the World Refugee Year schemes have now ended.

Obituary

JOHN PRESTON MAXWELL

M.D. Lond., F.R.C.S., F.R.C.O.G.

Prof. Preston Maxwell, who died in Cambridgeshire on July 25 in his 90th year, had spent the greater part of his working life in China, latterly as professor of obstetrics in Peking.

After qualifying from St. Bartholomew's Hospital in 1896, he took the F.R.C.S. in 1897, and then graduated M.B. in the University of London with a gold medal in obstetrics, and B.S. with first-class honours and gold medal. He proceeded, under the auspices of the English Presbyterian Missionary Society, to Yung-Chun, in South China and from there went to Yi-Yuan, not far from Changsha, the capital of Hu-nan Province. Here he was instrumental in building up an effective hospital which became known as "The Dr. Maxwell Hospital", or, in anglicised Chinese, "Ma Dai Fu"; and under this name the fame of the hospital and its director spread. In 1919 he was invited by the Rockefeller Foundation to come to Peking as professor of obstetrics and gynæcology in the then almost completed Peking Union Medical College. Before leaving Peking in 1937, he had held the post of director of the Medical College. His services to China were recognised by the award of the Order of the Splendid Jade.

E. W. H. C. writes:

"Energy and distinction were the hallmarks of Preston Maxwell's medical career. By his Chinese name he became known to countless hundreds not only because of his skill as a surgeon but because of his manifest love and admiration of the people of China. Here was a missionary and surgeon who did not need to preach concerning his Christian faith; in his daily life he was the very embodiment of it. He was a colleague and friend characterised, not only by brilliance in his profession, but by a quiet dignity, an unfailing energy in the service of others, and a deep knowledge of human character. To those, like myself, who knew him in China, his passing leaves a clear memory of a most gracious personality, of a colleague whose brilliance professionally was matched by his charm of manner, selflessness, and unfailing kindness."

Appointments

Liverpool Regional Hospital Board:

COHEN, R. I., M.B. Lpool, F.R.C.S., F.A.C.S.: consultant general surgeon, Newsham General Hospital.

HUMPHREYS, JOHN, CH.M. Lpool, F.R.C.S., F.R.C.S.E.: consultant general surgeon, Southport hospital group.

WAKELEY, J. C. N., M.B. Lond., F.R.C.S.: consultant general surgeon, Chester hospital group.

Manchester Regional Hospital Board:

MCCONNACHIE, R. W., M.B. Aberd., M.R.C.P.E., D.P.H.: consultant geriatrician, Blackburn and district hospital group.

WICKHAM, H., M.B. Lpool, F.R.C.S.: consultant E.N.T. surgeon, Preston and Chorley hospital group.

WILLIAMSON, P. J., M.B. Lond., D.P.M.: consultant psychiatrist, Stockport and Buxton hospital group.

YULE, J. H. B., M.CH. Oxon., F.R.C.S.: consultant surgeon, Blackpool and Fylde hospital group.

Western Regional Hospital Board, Scotland:

BLACK, W. P., M.B. Glasg., F.R.C.S.E., M.R.C.O.G., D.OBST.: consultant obstetrician and gynæcologist, Royal Infirmary and Eastern District Hospital, Glasgow.

ISAACS, BERNARD, M.B. Lond., M.R.C.P.: consultant physician, regional geriatric service.

ROBERTSON, J. M., M.B. Edin., D.P.M.: assistant psychiatrist, Bellsdyke Mental Hospital, Larbert.

SWINNEY, G. E., M.B. Aberd., D.P.M.: consultant psychiatrist and physician-superintendent, Woodilee Mental Hospital, Lenzie, Glasgow.

THOMSON, T. J., M.B. Glasg., F.R.F.P.S., M.R.C.P.: consultant physician, Stobhill Hospital, Glasgow, for duties at the Western District Hospital.

Births, Marriages, Deaths

WILKINSON.—On Aug. 1, to Clodagh (née Boyd), wife of Dr. J. B. Wilkinson, of 3, Greestone Place, Lincoln—a daughter.

Notes and News

THE OLDER WORKER

PREVAILING attitudes towards the older semiskilled worker have been studied in some of the larger manufacturing firms on Merseyside by the Medical Research Council's unit for research on the occupational aspects of ageing.[1]

Managers and foremen agreed that, of the changes that accompany increasing age, some are for the better (e.g., the older worker is more "steady" and more responsible) while others (e.g., slower movement and slower rate of learning) may impair efficiency. In the eyes of his superiors, the worker's skill, born of years of experience, often compensates for his slowing-up; but too little attention has been given to the fact that an ever-increasing strain is placed on the older man if he continues to do exacting work. While it is generally accepted in industry that middle-aged and older men should be transferred from physically heavy work, little is said about the unsuitability of work making a constant demand for speed or for close concentration.

The crucial age at which the effects of a demand for speed are felt is the late 40s or early 50s; but, because often the only alternative offered involves loss of status and loss of pay, many older men may remain too long at the job they are doing. For the semiskilled worker to find new employment in the second half of his working life may be difficult because he does not want to suffer loss of earnings while he becomes familiar with a new job, and because he may not relish the prospect of getting used to new faces and other ways. On the other hand his chances of getting new employment (even in his own firm) do not seem to be good after the age of 50. Consequently he is apt to go on until he can no longer make the grade, and then spend his last few years in a relatively menial occupation, and perhaps in correspondingly low spirits.

An increasing rate of technical innovation in industry may mean that a single group of limited skills will no longer last a man throughout his working life. Both this possibility and the present problems faced by the older worker point to the need for re-training, and this report suggests that industry should examine methods of training and re-training in relation to the special needs of the semiskilled worker after the age of 40.

WHOLE-TIME WORK IN A PARIS HOSPITAL

For a variety of reasons, France has been reluctant to accept the conception of whole-time service by consultants in hospital. By tradition, French consultants have devoted part of their time to hospital but have spent most of the day attending to private patients. The National Medical Association, which acts as intermediary between the medical profession and the public authorities, has been far from quick to accept the idea of whole-time service.

Professor Kourilsky's new book [2] gives his experience in the four years after he and his assistant undertook full-time work at the Saint-Antoine Hospital in Paris—a hospital which has 170 beds and deals with chest cases. The change, it seems, had remarkable consequences—an increase of about 72% in the turnover of patients, and a reduction of 51% in their average stay; a fall in bed occupancy from nearly 93% to 81%; and a fall from 6% to 3% in discharge against medical advice. The increased turnover led to an increased cost of maintenance per patient-day, but the cost of maintenance for the whole stay in hospital of each patient was reduced by 21%.

In France neither administrators nor doctors will be able to ignore this cool analytical approach to a subject which is rarely discussed without exciting passion. In this country it is of interest to know that arrangements in France are still so different from arrangements here.

1. Ageing and the Semi-skilled: A Survey in Manufacturing Industry on Merseyside, by ALASTAIR HERON and SHEILA M. CHOWN, assisted by M. S. Featherstone and Catherine M. Cunningham. Medical Research Council memorandum no. 40. H.M. Stationery Office, 1961. Pp. 59. 5s.

2. Kourilsky, R. Étude analytique de l'activité d'un service hospitalier Parisien à fonction plein temps. Paris: Association des Amis de l'Assistance Publique à Paris. 1961. Pp. 264. 12 N.F.

ADMISSION OF PATIENTS TO PSYCHIATRIC HOSPITALS

THE Joint Consultants Committee met in London on July 25, under the chairmanship of Mr. T. Holmes Sellors.

Representations have been made to the Ministry of Health that rigid zoning of catchment areas of psychiatric hospitals should be avoided. The committee realises that a hospital may not be in a position to accept a patient when requested if all beds are occupied or the case is unsuitable for that particular hospital, but this is a domestic matter and the advice of the consultants concerned would have to be sought. The Ministry has pointed out that defined catchment areas will be necessary for some years to come. It is essential that some hospitals should be responsible for compulsory emergency admissions. This and the uneven distribution of beds makes catchment areas necessary. In some areas hospital boards are very rigid in their application of catchment-area boundaries, but it is hoped that with the development of psychiatric units in general hospitals and the fall in demand for beds in psychiatric hospitals catchment-area arrangements can gradually be relaxed.

WORLD PSYCHIATRIC ASSOCIATION

AN International Society for the Organisation of World Congresses of Psychiatry has been in existence since 1950. This year, at the third World Psychiatric Congress held in Montreal in June, it was decided to change this organisation into a World Psychiatric Association, with functions of wider scope. The headquarters are to be in Geneva, and the first special general assembly will be held there next year.

The first officers of the Association are: president, D. E. Cameron (Canada); vice-president, F. G. Braceland (U.S.A.); general secretary, H. Ey (France); assistant secretaries, W. Sargant (Great Britain) and J. J. Lopez Ibor (Spain); and treasurer, P. Sivadon (France). A committee has been formed of 25 members from the participating countries.

University of Oxford

On July 29 the degree of B.M. was conferred on R. S. Cormack.

University of London

On June 21 the degree of M.D. was awarded to the following:

D. F. Eastcott, P. D. Meers, Felix Post, M. H. P. Sayers.

University of Birmingham

On July 14 the honorary degree of D.SC. was conferred on Prof. P. B. Medawar; and on July 15 Prof. James Mackintosh and Mr. Leslie Farrer-Brown received the honorary degree of LL.D.

Royal College of Surgeons of England

At a meeting of the council on Aug. 3 with Sir Arthur Porritt, the president, in the chair, Mr. R. L. B. Beare was admitted to the board of examiners in dental surgery (surgical section), and Dr. J. Alfred Lee for the fellowship on the Faculty of Anæsthetists. Sir Wilfrid Le Gros Clark was appointed the Edridge-Green lecturer for 1961.

Surgeon Rear-Admiral D. D. Steele-Perkins was admitted to the fellowship (ad eundem) and a diploma of fellowship was granted to Sim-Fook Lam.

Diplomas were granted, jointly with the Royal College of Physicians, to those mentioned in our issue of Aug. 5 (p. 326).

Faculty of Anæsthetists

Diplomas of fellowships have been granted to the following:

R. E. Graham, R. B. Roberts, W. D. Writer, Syed Ahmed Kabir, I. McI. Cochran, Barbara W. Cooke, R. E. C. Gibson, Jean M. Allison, C. J. Friendship, A. S. Gardiner, B. G. Pirie, Mendel Kaminer, C. G. Lloyd, R. E. Steele, P. O. Bodley, Ray McKenzie, G. W. Macnab, Eva R. Seelye, J. B. Burn, R. A. Butler, Phool Chandra, J. P. Davie, Shu Poh Ma, N. P. Murray, Margaret M. Voysey, Bridget A. Jepson, S. S. Lutchman, D. C. Maxwell, T. O. Ormston, Nalin Jagmohandas Paymaster, El Tahir Fadl, Arumugam Ganendran, G. B. Gillett, A. M. C. Jennings, H. G. Schroeder, J. H. L. Bland, A. V. Dreosti, Bruce Foster, S. M. Hart, D. A. Nightingale, J. F. O'Donnell, B. le G. Waldron.

Royal Medical Benevolent Fund

The annual general meeting will be held at 5 P.M. on Tuesday, Sept. 5, at the house of the Medical Society of London, 11, Chandos Street, W.1.

University College Hospital Medical School

Postgraduate demonstrations will be held at the medical school, University Street, London, W.C.1, on Thursday and Friday, Oct. 26 and 27. The annual dinner will be held at the Savoy Hotel, Strand, W.C.2, on Oct. 27, at 8 P.M. Tickets for the dinner (36*s*.) may be had from the hon. secretary, Old Students' Association, at the medical school.

Society of Apothecaries of London

Faculty of the History of Medicine and Pharmacy.—Applications are invited for the 1962 Maccabaean prize and medal, which are awarded annually by the faculty for an essay connected with the history of medicine or pharmacy. Particulars and entry forms, which should be returned by Oct. 15, may be had from the hon. secretary of the faculty, Dr. F. N. L. Poynter, Wellcome Historical Medical Library, Wellcome Building, Euston Road, London, N.W.1.

British Association of Physical Medicine

The annual meeting of this Association will be held on Friday and Saturday, April 27 and 28, at University College Hospital and the R.A.M.C. College, Millbank, London. Members wishing to read a short paper or show a film should submit the title, together with a brief abstract, to the Association, 47, Lincoln's Inn Fields, W.C.2, by Sept. 30.

Carlsberg-Wellcome Travelling Research Fellowships

The Carlsberg Foundation (Copenhagen) and the Wellcome Trust (London) announce the awards of these fellowships, which they jointly created in 1957.

The successful candidates for 1960–61 are Dr. Emil Poulsen, senior lecturer at the Royal Veterinary and Agricultural College, Copenhagen, who will work at the Medical Research Council's Toxicology Research Unit at Carshalton on the neurotoxic influence of alicyclic phosphates and similar compounds; Dr. A. F. Hayward, of the anatomy department of Glasgow University, who will work at the Carlsberg Laboratory in Copenhagen, under the direction of Dr. H. Holter, studying the electron-microscopic appearances in pinocytosis; and Dr. S. L. Rowles, a member of the external scientific staff of the Medical Research Council at the School of Dental Surgery in Birmingham, who will work with Dr. Tovborg Jensen of the Royal Veterinary and Agricultural College, Copenhagen, on the chemistry of the calcium phosphates with special reference to those in oral tissues.

Dr. B. C. Flather, of Newton, British Columbia, has been appointed M.B.E. in recognition of his part in rescue operations after a rock fall at the Home Sound Co. mine.

Dr. T. C. Gibson has been appointed assistant professor of medicine in the University of North Carolina, U.S.A.

Applications to attend a refresher course for consultant ophthalmologists, which is to be held at the Courage Laboratory of the Royal Eye Hospital, St. George's Circus, London, S.E.1, from Feb. 19 to 23, should be sent to Prof. Arnold Sorsby at the hospital before Dec. 1.

Courses on the rehabilitation of the amputee will be held for physical medicine consultants and geriatricians on Oct. 4 and 5, and for orthopædic consultants and senior registrars from Oct. 30 to Nov. 3, at the Limb Fitting Centre, Queen Mary's Hospital, Roehampton, London, S.W.15. Application should be made to the principal medical officer, Artificial Limbs and Appliances (Med. 7) at the hospital.

On Wednesday, Aug. 16, at 5.15 P.M., at the Royal Free Hospital, Gray's Inn Road, London, W.C.1, Dr. R. S. Yalow, of New York, will talk on assay of insulin.

On Tuesday, Aug. 15, at 5.30 P.M., at the Institute of Laryngology and Otology, 330, Gray's Inn Road, London, W.C.1, Dr. Barry J. Anson, of Chicago, will speak on features of otological anatomy contributory to problems in endaural surgery.

The Children's Hospital, Aghia Sophia, in Athens, which is a Greek pædiatric postgraduate school, is trying to establish a library, and would be grateful for back numbers of *The Lancet*, up to the beginning of this year. Offers of bound volumes, or complete half-yearly sets suitable for binding, should be sent to the library at the hospital.